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PULMONARY FIBROSIS: EXPERIMENTS OF SHORT DURATION.*

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It has been known for at least 4 centuries that men who inhale the dusty air resulting from certain industries suffer severely from respiratory disease, especially from tuberculosis. Heffernan, in considering the peculiar behavior of tuberculosis when associated with silicosis, wrote: "The total absence of conjugal infection among the wives and widows of the silicotic cases is on all fours with the oft-quoted observation of George Bauer, who wrote in 1557 that women could be found in the mining communities of the Carpathian mountains who had been widowed six times over by miner's phthisis." Throughout the present century investigations have been carried on in all the industrial centers of the world. It has been shown that the hazard of dusty atmosphere is pulmonary fibrosis and that different dusts possess different powers to excite and produce scarring within the lung. Silica is by far the most potent agent in the causation of silicosis and it has often been said that fibrosis of the lung is brought about "by any given dust so far only as this dust contains silica" (Riddell). Bohrod recalled that

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siderosis was the first form of pneumoconiosis to be described, and attributed the description to Zenker, who, in 1867, described 2 cases of what he termed siderosis. He proposed for the whole group of diseases caused by dust the term pneumoconiosis. Klotz, in 1914, showed that pneumoconiosis could be produced by inhaled particles of carbon, and that a severe type of fibrosis might be produced. The fibrosis was of the same type as that produced by silica, but required a longer time for its production.

The variations in the time required by atmospheres containing dust of known and constant nature, but of different concentrations, to produce fibrosis in the person employed, has led to a systematic study of industrial hazard. It was found that not only does silica cause a specific lesion, but that factors such as infection, size of dust particles, chemical reactions in tissue, solubility of dust particles, moisture, hygienic environment of the men, races of men, nationality, and interruption of work, all played parts in the production of the fibrotic lesion or influenced its progress or its prognosis.

It has been proved[4] that there are certain limitations of permissible dustiness in the dangerous trades, and the figure that has been more or less arbitrarily chosen is 10,000,000 particles for each cubic foot of air. Observers have shown that the injury produced is in direct ratio to the numbers of dust particles and that, if this number is more than 20,000,000 particles for each cubic foot of air, the risk of the development of fibrosis and of its most important and most common complication, tuberculosis, grows into a really serious menace. It is assumed, in any statement of this kind, that not only the percentage of silicon is high but also that from 50 to 70 per cent of the particles of dust are smaller than 10 microns in diameter. In men examined in The Mayo Clinic who had been subjected to dusty atmospheres, the length of time required for the breakdown of the protective mechanism, and the consequent production of fibrosis, varied, except in exceptional cases, over the wide limits of at least 5 to 15 years, depending on many physical, chemical and bacterial factors. Furthermore, experiments on animals subjected to a dusty atmosphere have almost uniformly failed to produce a condition comparable to the fibrosis of silicosis.[1] For these reasons, study of the mechanism of the production of this pathologic state becomes at once very difficult. In man, the end results of fibrosis and of tuberculosis have been thoroughly studied, and the clinicopathologic picture has been well described. Less exact information is available regarding the pathologic processes, from the earliest evidence of failure of the protective forces to rid the lung of its load of dust, to the full development of the protective mechanism that attempts to dissolve, destroy, remove or mobilize the irritant and encapsulate it, resulting in the production of the dense fibrosis of the silicotic lung.

Landis[9] wrote: "The solution, I think, lies in the fact that the

area is at first protected by the cilia of the outer respiratory tract. Gradually these defenses break down and the small particles of dust are taken up by the lymphatics and appear in the alveolar cells, the first histologic change noted being the swollen alveolar cells. Other changes are marked swelling of the cells lining the alveoli, with marked pigmentation in the alveolar walls in and about the bronchial walls. Deposits of dust seem to localize at the junction of the lymphatic channels. The cut surface will show this in the gray parenchyma of the lung. This represents the stage of pneumoconiosis, and with the definite deposits of these small points of dust one begins having a marked inflammatory condition of fibrous tissue. The fibrous tissue and the dust alternate, the points coalesce and ultimately there is a large fibrous mass."

Experiments done in 1925[10] on the aspiration of particulate matter into the lung, proved that the technique then employed permitted particles of very small dimension, comparable to the particles of silica that effect the pulmonary changes in cases of silicosis, to reach the alveoli, alveolar walls, and subpleural spaces, within a period of 40 minutes. By this simple technique, therefore, we were able to circumvent the experiments of long duration, in which dusting had been employed, and which had failed because of the protective mechanism that rids the lung of foreign particles and that does not permit them to reach the finer bronchioles or the alveoli. It is the material that cannot be removed from the lung that does the mischief, not the material which soon after entrance is removed from the lungs. By administering the foreign material in the form of a suspension, the primary mechanism of removal was at once overcome, and the particles were placed so deep in the bronchi and the alveoli that the secondary process of protection of the lung from injury was promptly mobilized and started into activity. This mechanism was defined by Maximow as follows: "All multicellular organisms are endowed with the ability to repair damages inflicted by extraneous factors and autogenous disturbances to resist, neutralize, digest or destroy noxious agents which endanger the normal course of life and to eliminate them. The connective tissue, the so-called 'mesenchyme' plays the predominant rôle in these defense reactions."

The worker in the dusty atmosphere of the dangerous trades is unharmed as long as the dust can be satisfactorily removed by the cilia of the outer part of the respiratory tract, and he becomes injured when that mechanism of protection breaks down and dust reaches the alveoli. It was possible to produce, within a brief period, comparable loss of competency in the normal defense mechanism in an animal. For these reasons it was thought probable that the endowment to repair, resist, neutralize, digest, or destroy might be studied, and that the facts obtained might be used to explain the production in man of silicosis.

Experiments. In the first experiment the dog lay on an inclined plane with the head of the table elevated 10 cm. higher than the foot. The head was held to one side. Forty cubic centimeters of a mixture of 20 per cent barium and India ink was given in doses of 5 cc. every 5 minutes. It was simply dripped into the mouth and allowed to flow down the cheek. The dog was kept anesthetized with ether throughout the experiment, and the suction of inspiration was the only force employed to transport the suspension of particles down to, and through, the trachea into the lungs.

At the conclusion of the experiment the dog was despatched by overetherization, and necropsy was done at once. When the trachea was opened, mucus that was stained black could be seen within the trachea. It extended downward, past the carina, into both main bronchi, and the major portion entered the lower lobes of the lungs. More found its way into the right side than into the left and only small amounts were transported into the upper lobes. Within the lower lobes, the mucus, laden with particulate matter, passed so deeply into the bronchial divisions that the bronchi were too small to allow the finest scissor points to be inserted into their lumens for further opening of their walls. However, by gentle traction, tenacious threads of mucus, blackened by India ink, could be extracted.

The cut surface of the lung, in its distal parts, was mottled with tiny black spots which represented the finer bronchial divisions. In many instances these were removed, in part by cohesion and traction, and by this means could be distinguished from any possible effect of anthracosis. The pleural surface was mottled with blackened areas which were separated from each other by visceral pleura of normal color.

Microscopically there was no possible confusion between the anthracosis normally present and the pigment artificially introduced. The former presented the characteristic appearance. The granules of carbon were intensely black and were so densely packed within cells that the nature of the phagocytic cell could not be determined. These were grouped in the characteristic fashion about bloodvessels and bronchi and served to identify the presence of the small bronchioles. Carbon was not found in the alveolar walls, but a linear distribution could be seen in the subpleural spaces. This description is similar to that of the lymphatic system of the lungs and pleura.[2,6,12] It is in the lymphatic spaces and tissues that impounded particulate matter is stored. It is impounded and stored when the lymphatic system fails in its function of removing fluid, and especially in its function of removing particulate matter.

The appearance, after the artificial introduction of foreign matter, was decidedly different from that of anthracosis. The suspension of barium, 20 per cent, colored with India ink, was chosen because the particles were many times smaller than blood cells, because

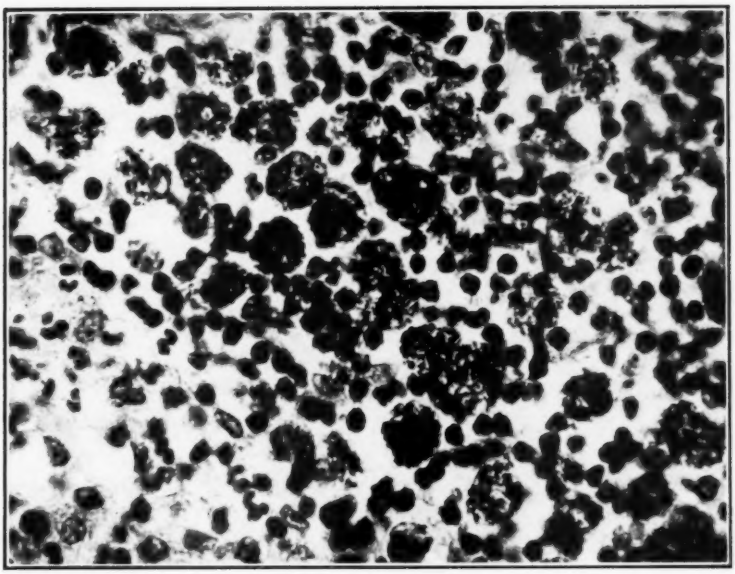

FIG. 1.—Nongranular mononuclear phagocytic cells known as histiocytes, clasmatocytes or polyblasts. The cells show marked evidence of phagocytosis; they are from trabeculæ of a peritracheal lymph node and reached the node one and a half hours after intratracheal administration of particulate graphite.

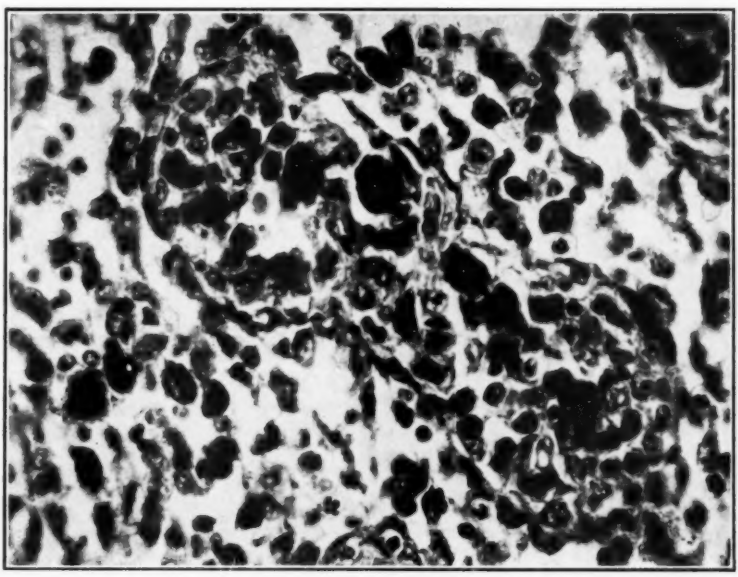

FIG. 2.—Peritracheal lymph node after absorption of colloidal iron from the lung. The node is filled with phagocytic cells containing iron. Littoral cells are filled with iron; evidence of early fibroplastic action.

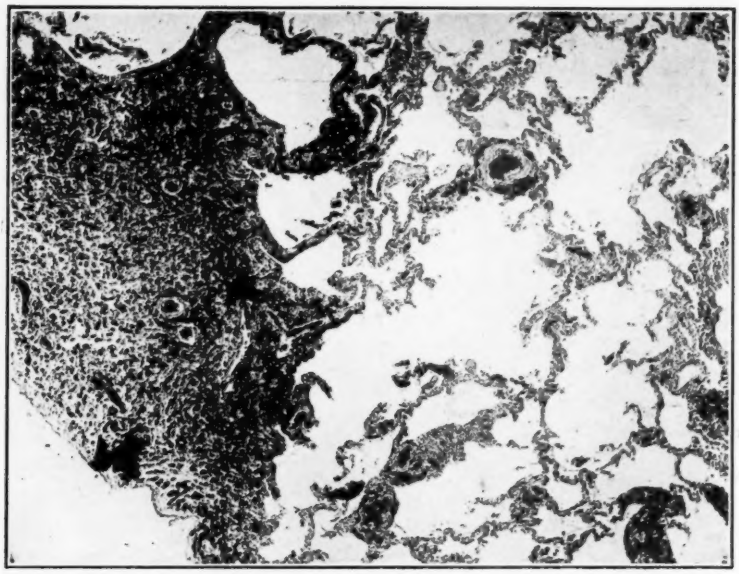

FIG. 3.—Tissue from lung of human being, with a localized subpleural fibrous tissue plaque, in a case of anthracosis. Storage of carbon has taken place in perivascular and perilymphatic spaces. There is evidence of slight reaction in the alveolar walls, emphysema.

FIG. 4.—Tissue from lung of a quartz miner. Dense fibrous tissue is present. The alveolar walls are markedly thickened and the contained capillaries are compressed. The cells lining the alveoli are cuboidal and desquamation of them has taken place, giving rise to the so-called dust cells, which permit of continuous evacuation of silicon from the lung. The fibrosis extends throughout the parenchyma, far removed from the perivascular and peribronchial lymph depots. There is a high degree of emphysema.

microscopically they were much lighter in color than the carbon seen in anthracosis, and because the two could not readily be confused. On studying the sections, it became apparent that within 40 minutes the force of aspiration had carried foreign material from the mouth into the bronchial tree and into the alveoli, and thence a migration had occurred which transported the particles into the alveolar walls and to the periphery of the lung, in which, beneath the superficial layer of the pleura, the India ink and barium could be identified.

Within the hour taken to perform the experiment, particulate matter had been placed as deeply in the lung as any dusting experiment could have placed it in months, and probably as deeply as man would have inhaled it after even years of exposure to an atmosphere heavy with the dusts considered dangerous in industry. We were thus permitted, by overcoming the first protection afforded by the cilia of the upper part of the respiratory tract, to see the first stage of the second protective mechanism, which is called into service when dusts can no longer be removed by ciliary transportation of dust-laden mucus.

The second stage of protection depends on the ability of the lung to repair injury after the first mechanism has been overcome. Then the defense reaction is taken up by the mesenchyme, and the offending foreign bodies are destroyed or removed from the organ through the lymphatic structures, or are stored in depots where they are so invested that they do the minimal amount of harm. The process is, first of all, one of phagocytosis; later, one of lymphatic drainage and, finally, one of fibrosis to encapsulate what cannot be removed.

Much of this second protective mechanism is not thoroughly explained. We believe that the part played within the lung by the mesenchyme is as follows:

The exact origin of the phagocytic cells of the lungs is still in question. Hitherto they were thought to be of endothelial origin. This was at the time the endothelial origin of phagocytes in general was accepted. Since this general hypothesis has been dethroned, concepts of the origin of the phagocytic cells in the lung have changed. The present concept is essentially that they are derived from the mesenchyme. It is thought that these cells arise from primitive mesenchyme cells which lie within the interalveolar septums and increase in number as the demand arises. The changes in our concept concerning the origin of the phagocytic cells in the lung coincide essentially with the changes in our belief regarding the morphology of the alveolar cells. In fetal life the alveolus is lined with a cuboidal type of epithelium. Subsequently this epithelium is lost and the alveoli then come to be lined by a flattened layer of cells which are now said to be derived from the mesenchyme. The exact fate of the original embryonic epithelium is not known. The mature alveolar cells of mesenchymal origin are potential his-

tiocytes, so that as the occasion demands, these cells may enter the lumen of the alveolus and phagocytose débris or foreign particles. These lining histiocytes are probably identical with the cells that lie within the septums; therefore as a shedding of lining histiocytes occurs, other histiocytes, from the septums, take their place. These cells, as they enter the lumen of the alveolus, phagocytose foreign particles, pass back through the wall of the alveolus or the bronchiole into the substance of the lung, and either migrate directly through the parenchyma, or enter lymph tracts and proceed to the regional lymph nodes.

In this respect, then, we may say that alveolar phagocytes, or the pulmonary dust cell, or the so-called heart failure cells, are nothing more or less than normal histiocytes, comparable in every way to those which abound throughout the body generally. They are derived from the mesenchyme, may migrate freely through the pulmonary parenchyma, and are concerned functionally with the defense mechanism of the organ.

In our experiment we were able to demonstrate particulate material in the farthest reaches of the lung. When microscopic slides were prepared and examined, the mechanism of migration from the air tubes into the parenchyma of the lung became apparent.

Aspirated material could readily be distinguished in the smallest bronchial divisions. It was mainly in a free state, but mononuclear phagocytic cells could be seen scattered through it; these were invariably loaded with particles. In some instances the foreign particles were literally packed in the cell in such amounts that the identity of the cell itself became difficult to determine. The same type of phagocytic cell was seen within the alveoli and in the alveolar walls, and their migration could be followed as far as the subpleural spaces, in which they were sometimes arranged in a linear fashion, suggesting their inclusion in lymphatic spaces. Particles in a free state were also found in the alveolar walls. Presumably they had penetrated the alveolar lining and presumably also they later were engulfed by phagocytic cells of mesenchymal origin known under different names, histiocytes, clasmatocytes and polyblasts.

Curiously enough, there was little evidence that polymorphonuclear leukocytes had migrated from the bloodvessels. Ordinarily we have learned to expect them to be the first phagocytes seen in inflammation produced by the introduction of sterile particulate material. The usual influences of attraction, whether chemotactic, osmotic, or electrotropic, enumerated by Maximow, failed to introduce these cells and permit them to take on themselves the first burden of phagocytosis. In our experiments[6] dealing with pleural exudation, polymorphonuclear leukocytes were the first phagocytes to appear, and as they withdrew from the exudate, or disintegrated, monuclear cells of polyblastic type, which we have

called clasmatocytes, appeared later and continued the phagocytic function.

The phagocytosis under discussion was, however, essentially confined to mononuclear cells, identical in appearance with the clasmatocytes we have described in our work with pleural exudates.[6]

In the second experiment a half-grown puppy that had lived in the country was chosen so that all risk might be obviated regarding the confusion of foreign particles artificially introduced with those present in an anthracotic lung. A colloidal suspension of graphite was introduced into the trachea, and 1½ hours later necropsy was performed. The lower lobes of the lung had received almost the whole amount of the suspension of graphite. A few small regions of infiltration occurred in the upper lobes. These portions of the lung into which the graphite had been aspirated were swollen, edematous, and black. Examination of the gross specimen disclosed that the graphite had filled the entire bronchial tree. Examination of microscopic slides revealed that the same mechanism of mononuclear phagocytosis had operated in this animal as in the first, to carry the particulate matter throughout the pulmonary parenchyma and to the subpleural spaces. Polymorphonuclear leukocytes were seen in relatively small numbers, but they were definitely phagocytic in action.

Moreover, a further phenomenon in protective processes appeared. There were indefinite, blackened lines in the visceral pleura, that were densest at the hilum of the lungs, and the tracheobronchial lymph nodes were enlarged and very densely blackened. This mechanism for removal of obnoxious particles was entirely confined to the lymphatic system. The bloodvessels did not contain phagocytic cells which had engulfed particles of pigment. The lymphatic system had evidently begun functioning early, because, even after 1½ hours, the graphite had not only reached the tracheobronchial nodes, but had blackened the paratracheal nodes. The node commonly found in the dog opposite the first rib was deeply blackened. It is only a short distance removed from the confluence of its efferent lymph vessels and the venous system.

Fixed sections of the inferior tracheobronchial nodes, of the superior tracheobronchial nodes and of the paratracheal lymph nodes, were examined microscopically. The central portion of the glands, mainly the trabeculæ, were seen, on low-power examination, to be filled with graphite. On increasing the power of magnification, the graphite was found to be entirely phagocytosed, mainly in markedly enlarged nongranular mononuclear cells; a few polymorphonuclear leukocytes took part in the phagocytic action and were loaded with particles of graphite. It was apparent that the mesenchyme had taken on itself the function of protection.

After phagocytosis had occurred, the lymphatics had rapidly conveyed the cells, with their débris, out of the lung. Within

1½ hours these were as far removed as the farthest lymph node in the lymphatic system leading to the lymphatic-venous juncture.

All of the bloodvessels of the lung and the nodes were free of pigment and of pigment-bearing cells.

The liver had felt the influence of irritation from foreign bodies. Kupffer cells were enlarged and swollen, showing evidence of histiocytic activity.

Comment. In our other experiments,[7] in which the tracheobronchial and the paratracheal glands have become filled with absorbed material from the pleural space, a similar reaction occurred in the reticulo-endothelial system, especially of the liver. The Kupffer cells became enlarged and bulged into the sinusoids. The reaction seemed to be one of stimulation due to the influence of foreign material, and always preceded the phagocytic phenomenon which occurred after the lymph stream had commingled with the blood. Then débris and particles were ingested by the Kupffer cells. The final disposal of particles engulfed by the Kupffer cells is not known. Presumably the Kupffer cell itself is transformed into a fibroblast or is destroyed.

When the conveying mechanism fails and débris cannot be carried out of the lung, Nature stores it in convenient depots and sets about to make it harmless. Since the whole process of removal is carried on by the lymphatic system, it is obvious that the storage should be within that system. Therefore the walls of the bronchi, to their finest divisions, the ductuli alveolares, have their lymphatic spaces crowded with unremoved cells containing intracellular particles. The lymphatic tissue at the bronchial divisions, and the lymph vessels surrounding the arteries and veins, all bear their load of phagocytic mononuclear cells filled with débris, and the subpleural lymph channels are similarly filled.

The first step toward the formation of fibrous tissue, and the last toward protection, is now ready to start. We have found that fibrosis began early in the mediastinal tissues which had taken within themselves the graphite-laden phagocytic cells of pleural exudates. We noted that the polymorphonuclear leukocytes, which had reacted first as phagocytic cells, broke down or disappeared, and that the mesenchyme cell, the clasmatocyte or histiocyte, or resting wandering cell, or mononuclear exudate cell, or polyblast of Maximow, increased in numbers as time elapsed. These are all names of the same cell in different states of activity. They seemed most active in removing the cause of the inflammatory irritation and clearing the tissue of débris. They were not only in large numbers, but they were densely crowded with particles, and did not appear to degenerate and break down readily. By the fifth day, they seemed to elongate and form fibers, and seemed actually to become transformed into cells resembling fibroblasts. The fixed tissue cells, or fibroblasts, were rarely phagocytic and reacted slowly, becoming

enlarged as did the Kupffer cells in the liver, and proliferated. Together, these transformed clasmatocytes and fibroblasts became part of granulation tissue which later developed into true scar tissue.

A similar process occurs within the lung. The degree of fibrosis, however, is dependent on the nature of the phagocytosed irritant, and explains the difference in the amount of fibrosis seen in the lungs of workers in soft coal and those who have spent a much briefer time in a much less dusty atmosphere of the quartz mine. Up to the stage of fibrosis, the mechanism is the same. The fibroblasts provide a fibrous capsule which invests the irritant substance that remains, as yet intracellular, and when the irritation is prolonged or continuous they proliferate to such a degree that actual induration occurs. It seems probable that the phagocytic cell elaborates some substance that attempts to destroy or liquefy its load of débris. Maximow expressed the belief that this may be an enzyme or other soluble substance. It is at this point that bacterial, mechanical or chemical differences in the ingested material control the degree of succeeding fibrosis. Gye and Kettle have attempted to explain why silica is conspicuous and is possibly alone among common dusts in its capability of inducing extreme degrees of fibrosis. They wrote: "The view most often expressed is that silica owes its injurious quality to its physical properties. Moore tabulates the properties as follows: (1) Its heaviness; (2) its sharp, vitreous fractures, and (3) its great hardness and insolubility. Hardness, heaviness and sharpness of points or edges are properties which lose their significance when applied to particles of dust enclosed in the cytoplasm of wandering cells; direct mechanical injury to the lung (under the circumstances by which the dust gains access) is almost inconceivable. The property of insolubility deserves more attention. Silica, though insoluble in all acids, except hydrofluoric, is readily dissolved in alkalis. The statement, therefore, that silica dust is insoluble is only partially true, and the conditions under which a solution may be obtained are relevant to the problem of silicosis. Carbon particles, certainly in a test tube, are more insoluble than silica particles, and it is universally agreed that carbon dust, unless in large amounts, is of no pathologic importance. In silicosis the injury to the lungs is a continuous process, and the amount of fibrous tissue formed is much greater than can be explained upon the mechanical process involving disturbances of microscopic anatomic relationships. Further, the fibrosis extends far beyond the near neighborhood of the silica particles." In the report of the committee on silicosis presented to the Industrial Hygiene Section of the American Public Health Association, Minneapolis, Minn., October 4, 1929, a similar view is expressed:

"According to Heffernan on the biophysics of silica and etiology of silicosis, the disease is the result of the local action of hydrated silica upon pulmonary tissues; the action is physico-chemical in

nature and its development depends upon the rapidity with which fresh silica hydrosol is brought into contact with pulmonary tissue; substances such as alkalis, which favor the formation of silica hydrosol from silica, when added to silica dust accelerate the development of silicosis; and substances such as carbon coal dust or clays, which retard or prevent the formation of hydrosol from silica or which coagulate the hydrosol when formed, retard or prevent silicosis."

A more recent communication regarding the chemical reaction of silica on the tissues has been made by Mills. As a result of his investigations on Spongilla fragilis he concluded: "The spicules of the fresh-water sponge, Spongilla fragilis, are composed of opal, a form of hydrated silica, which is similar to quartz in its chemical reactions. These spicules, when introduced into the tissues of animals, are slowly but definitely dissolved, proving conclusively that silica is soluble in the tissue fluids of animals, and presumably of man. This confirmed the assumption held by many students of silicosis that particles of siliceous material are gradually converted into the colloidal state and as such exert a fibroplastic influence on the lungs of miners and other exposed industrial workers. Definite fibrosis of the lung of a dog into which the spicules had been introduced suggests that there is a concomitant injury attributable to the disappearance by solution of the siliceous elements of the spicules."

It seems probable, then, that the final process is a chemical one which occurs within the cell. The "enzyme," or soluble substance elaborated by the phagocyte, fails to dissolve the particle of carbon, which is therefore bland and nontoxic, and can be stored without destructive tissue reaction appearing, and stimulating continuous hyperplasia of fibroblasts and late transformation into scar tissue. The phagocyte, by the chemical action of its elaborated substance or enzyme, seems, however, to produce a tissue poison from the particles of silica, and this process continues as long as silica remains in the lung. It is slow but continuous and stimulates constant hyperplasia of fibroblasts and constant addition to the amount of scar tissue. It is the explanation of the fact that men may lose respiratory competency years after having been engaged in work which is done in a dusty atmosphere, in which there is a high percentage of silica.

The specificity of silica, therefore, seems to be due to its transformation within the cell from inert particles to a substance that is a protoplasmic poison. Gye and Kettle have expressed their view as follows: "Our work has been based on the known facts: (1) That colloidal silica is a cell poison; (2) that colloidal silica is the most easily formed soluble form of silica, the circulation of silica in nature depending on this, and (3) that living matter (soil bacteria) is able to break up mineral silicates with the formation of

soluble silica. We judged it probable that the fibrosis brought about by finely divided silica was due to the slow formation in the tissues of silica sol, either directly or through the intermediate formation of sodium silicate, which is decomposed by carbonic acid, the solution formed acting as a cell poison."

It is probable that other inorganic substances may produce protoplasmic poisons when chemical reactions occur within the cells. We have in progress at present experiments in which we are using colloidal iron in a similar way to that described in the protocol of the experiment in which graphite and India ink were employed. Within 12 days we have observed early but widespread and definite fibrosis in the lung.

The Kupffer cells of the liver, the littoral cells of the paratracheal lymph nodes, the cells of the tubules of the kidney and of the cortex of the suprarenal glands all contained iron. There was, also, definite evidence of injury to the cytoplasm, both in the lymph nodes and in the liver.

Conclusions. It seems probable that the fibrosis of the lungs produced in workers exposed to dusty atmospheres, especially those in which fine particles of silica make up the larger percentage of the dust, is an end product and represents a progressive defeat of the protective mechanisms of the body. It is never found until the lung fails to rid itself of dust carried out of the bronchi by ciliary action or of dust carried through the lung by way of the lymphatic channels. With the breakdown in the carrying mechanisms, the burden of protection is the phagocytic cell, which, with its load of engulfed material, passes to all parts of the lung and ultimately becomes immobilized in those portions of parenchyma in which lymphatic tissue is abundant. The cells concerned are polymorphonuclear leukocytes, which are the first to appear, to disintegrate and to disappear, and clasmatocytes, which appear later, are extremely active, break up less readily, and may become transformed into fibroblasts. In association with the tissue fibroblasts the clasmatocytes form scar tissue.

Finally, fibrosis is the result of the action of substances secreted by the cell on the foreign particles. If a tissue poison results from this chemical action, fibrosis is encouraged, and is progressive, lasting as long as the unaltered irritant remains in the lung.

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BENIGN TUMORS OF THE BRONCHUS.

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The following study of benign tumors of the bronchus is based on 17 cases, 14 of which we have observed clinically and bronchoscopically with biopsy. The remaining 3 belong to an earlier period and are derived from the clinical and autopsy records of Mt. Sinai Hospital. We have included 2 cases of inflammatory polyp and 1 case of bronchial lymphoma. This has been done intentionally and may be justified in a study which is essentially clinical because these cases present the same problems in diagnosis and treatment as benign neoplasms and they have a similar pathogenesis.

These tumors, of which not more than 30 have been recorded.[1]* possess a practical importance which outweighs their rarity. Chevalier Jackson[2] states that primary growths of the tracheobronchial tree though not frequent are by no means rare. Although they are characterized as benign, this is true only in a pathologic sense. If they are not discovered and removed they produce pulmonary complications which result in the death of the patient as surely as if they were truly malignant. Furthermore, we have

* The reader is referred to this article for a brief survey of the literature.

FIG. 1.—Benign tumor of the bronchus. Low power.

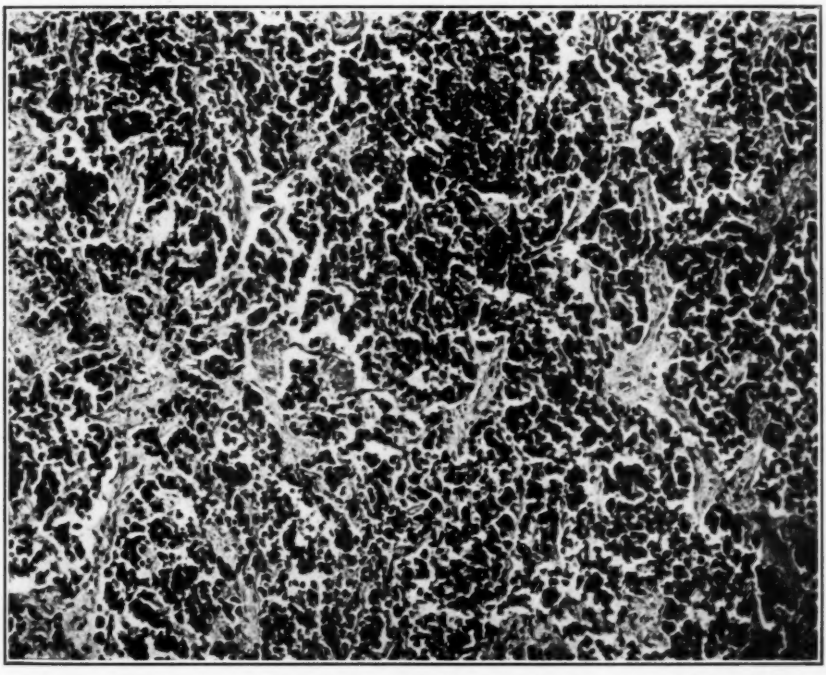

FIG. 2.—Benign tumor of the bronchus. High power, showing characteristic cellular structure.

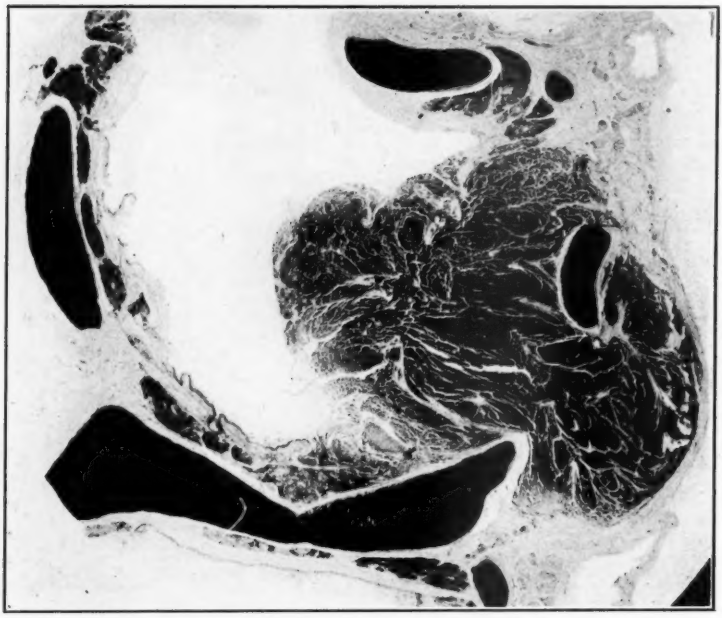

FIG. 3.—Cross section of bronchus. Moderately enlarged, showing entire polyp. Note the extension of the adenoma between and behind the cartilages.

FIG. 4.—Adenomatous polyp in left main bronchus. Showing characteristic position; dilatation and infection of the distal bronchus and lung.

definite evidence which will be later adduced, that a benign bronchial tumor may years later undergo malignant degeneration. On the other hand if they are early recognized they are very amenable to treatment. For these reasons we present a pathologic study and clinical analysis of our cases and have attempted to formulate the data upon which a diagnosis may be made clinically. That this can be done with some measure of success is indicated by the fact that of the 14 cases which we personally studied a presumptive diagnosis was correctly made in 9 cases on purely clinical grounds.

Pathology. We preface the clinical features of benign tumors of the bronchi with an outline of the essential pathologic facts. Our observations are limited to the form of tumor known as the adenomatous polyp, as this is the commonest type of bronchial tumor and comprises 12 of our cases. Other types of tumors are occasionally found. Jackson[2] describes primary papillomata and fibromata. He also points out the tendency toward malignancy which is evidenced by some chondromata and osteochondromata.

Adenomatous polypi always originate rom the mucous membrane of a large or main bronchus. The growth is commonly situated not far from the origin of the bronchus. It is usually pedunculated and is so placed that its free bulbous end is directed toward the trachea. This position is a consequence of its extrusion from its bronchus in the act of coughing.

The body of the tumor is usually oval, its shape being determined by the length of its pedicle and the caliber of the bronchus to which it adapts itself and which it completely fills. If the pedicle is long the tumor may be movable and thus, acting as a ball valve, produce obstruction either of the trachea or of a bronchus other than that from which it takes its origin.

Microscopic Pathology. The body of the tumor has a smooth surface and is covered by a layer of epithelium. This often shows a squamous metaplasia which may result in a hornified stratified covering. In the basal part of the tumor where it is attached to the bronchial wall, the epithelium may be normal or it may be made up of a stratified layer of columnar epithelium. Beneath this there is a completely intact basement membrane. Subjacent to the latter there is often a layer of loose connective tissue within which are numerous dilated bloodvessels. Erosion of these vessels often gives rise to bronchial hemorrhage.

The tumor itself is made up of rather small cells whose cytoplasm varies in size in different cases. The nuclei are usually small and either perfectly round or ovoid. Their striking characteristic is a uniformity and hemogeneity of structure and staining qualities. They are usually arranged in acini with perfectly definite basement membranes. There are instances, however, in which the acinar structure is not present and the cells appear to form solid masses. In the process of fixation and embedding there is a tendency for

the cells to retract from the basement membrane which is perhaps more marked than is the case in most adenomatous tumors. (Figs. 1 and 2.)

This description of the minute pathology of benign adenomas accords in its essential features with that of a small number of similar cases which have been recorded in the literature as carcinomas. It is our belief, based on the clinical and pathologic study of our patients and a comparison with those reported, that a number of these reported cases were mistakenly considered carcinomas and that they were truly benign adenomas. In their microscopic reports the authors frequently pointed out that there was an infiltration of the submucosa between the cartilaginous rings which sometimes extended even behind the cartilages. This was regarded by them as evidence of malignancy. However, when one studies the anatomic position of the bronchial glands, it will be found that they are normally found not only on the internal aspect of the cartilages, but also between and externally to them. The presence of neoplastic tissue in these locations therefore does not signify malignant infiltration of the bronchial wall but results from the hyperplasia of normally situated glandular structures. (Fig. 3.)

In 2 of our cases which were studied postmortem, there was some evidence of infiltration of the deeper tissues of the polyp. This consisted of a few groups of cells which apparently lay in a stroma outside the glandular acini. In these cases the distinction between a benign and a malignant neoplasm becomes more difficult. On purely pathologic grounds, they would have to be regarded as carcinomas. On the other hand, both cases presented a long history of pulmonary disease and there was a total lack of any gross infiltration of the bronchi or the lungs which should have been present if they had been malignant. For these reasons the microscopic interpretation of material removed through the bronchoscope or even at autopsy must be made with considerable reservation and with due regard to the clinical findings. It is of course possible in the occasional case which shows this beginning infiltration of the stroma that the adenoma is in the process of transition to carcinoma. Such a coincidence is certainly conceivable and we have 2 cases which are fully described at the end of this paper in which this sequence of events probably took place.

The point of origin of benign adenomas has been in dispute. There are 3 structures in the bronchus from which they could arise namely, the bronchial epithelium, the mucous glands or the duct epithelium of these glands. The bronchial epithelium can be definitely excluded as the origin of the tumors because the latter are invariably covered by this epithelium and by an intact basement membrane. The tumors probably do not begin in the mucous glands as their cellular elements bear no resemblance to those of the glands. We have in fact, observed the mucous glands to be dis-

tinct from the tumor with no apparent transition into it. This leaves the duct epithel um as the probable point of origin of the tumor. The tumor cells closely resemble those of the ducts of the mucous glands and in 1 of our cases there was distinct evidence of proliferation of the ducts. In parts of the tumor there were dilated ducts which had undergone squamous metaplasia so that some of the acini were composed of stratified squamous epithelium.

In addition to the adenomatous tumors which represent the large majority of our cases, there are recorded in the literature fibromas, fibrolipomas and enchondromas. Although pathologically distinct from adenomas they are similar to them in their mechanical effects and symptoms.

The cases which we herewith report are summarized in the following table:

TABLE 1.—SUMMARY OF 17 BENIGN TUMORS OF THE BRONCHUS.

Case No.	Age.	Sex.	Type of tumor.	Duration.
1	28	M	Fibroma	1 year
2	35	F	Adenoma	13 years
3	18	F	Adenoma	5 "
4	26	M	Adenoma	3 "
5	26	M	Inflammatory polyp	9 months
6	48	M	Fibrolipoma	1½ years
7	47	F	Adenoma	5 "
8	30	F	Adenoma	11 "
9	64	M	Adenoma	30 "
10	35	M	Inflammatory polyp	5 months
11	54	F	Adenoma	3 years
12	62	F	Adenoma	6 months
13	32	F	Lymphoma	1½ years
14	48	M	Adenoma	2 weeks (?)
15	35	M	Adenoma	(?)
16	32	M	Adenoma	7 years
17	35	F	Adenoma	2 "

The cases are almost equally divided between males and females.

TABLE 2.—AGE INCIDENCE.

Age.	No. of cases
10 to 20 years	1
21 to 30 "	3
31 to 40 "	7
41 to 50 "	3
51 to 60 "	1
61 to 70 "	2

It will be seen that two-thirds of the cases occur before the age of 40 years.

CLINICAL COURSE. The key to an understanding of the clinical course of this disease in its various forms is a knowledge of the mechanical effects of endobronchial tumors of this type. Such effects of course will be entirely absent while the tumor is still small. There is every reason to believe that a benign tumor, if its growth is slow, may exist for years within a bronchus without betraying

its presence by any symptoms, even cough. However, owing to its vascularity, at any time during its growth there are apt to be recurring hemorrhages from the bronchi unassociated with any other symptoms. Hemoptysis, which is most characteristic of benign tumors occurred in 12 of our cases and was usually frequently repeated. In a number of cases it occurred for periods of 1½ to 5 years and in one instance it was frequently repeated for 30 years. In this stage of the disease which may be called its nonobstructive phase because there is no occlusion of the bronchus, pulmonary tuberculosis is usually suspected because of the hemopytsis.

The really serious symptoms, those which are apt to bring the patients under observation, are due to the continued growth of the tumor which ultimately causes an obstruction or occlusion of a large bronchus. The consequences of such an obstruction are various and they depend upon the advent of infection which is rarely long absent when a bronchus is occluded. It therefore happens that the majority of cases with benign tumor presented themselves with symptoms of bronchial and pulmonary infection which had lasted for months or years. The essential clinical facts in our cases are summarized in the individual histories at the end of this paper. From these histories the following facts may be derived:

1. The first symptom may be an attack of pneumonia with or without pleurisy (Cases 1, 2, 3, 4, 7). We may assume that this was preceded by an atelectasis of the lung due to stenosis of a bronchus upon which the pneumonia was engrafted. Usually this initial pneumonia subsided and was succeeded by a stage lasting several months to 6 years during which there were no symptoms at all or cough with blood expectoration.

2. In 3 cases the initial symptom was a dry pleurisy (Cases 13 and 5) or pleurisy with effusion (Case 6) which occurred respectively 1½, 5 and 13 years before. This was followed by a period of several years during which there were no major symptoms. We must here assume that the bronchostenosis gave rise to a low-grade infection of the lung with an inflammation of the pleura. After a variable lapse of time these cases progress to present the changes of the advanced stage of the disease.

3. Purulent infection of the pleura occurred in 3 of our cases. It is a direct consequence of suppurative disease of the lungs and as such usually is a complication of the later stages of the disease. In our 3 cases the existence of an underlying bronchial tumor was not suspected in spite of a previous history of cough and expectoration. The patients sought treatment because of the acute condition of the pleura which required surgical treatment. The bronchial tumors were discovered only at autopsy. In 1 case (Case 14), the empyema appeared to be the first symptom of the tumor. Although the history of only 2 weeks' duration is open to doubt, the fact remains that a bronchostenosis with suppuration of the lung must

have been more or less latent for some time and that no major symptoms were produced until the pleura was infected. In another case (Case 5), an empyema which had been drained some time previously continued to discharge pus and failed to close up because of an unrecognized tumor of the bronchus.

4. The inevitable termination of all cases of bronchial tumors, whatever their initial symptoms, is suppurative bronchiectasis and suppurative or indurative pneumonitis which are always found if the obstruction is not relieved in time. Apparently, the atelectatic lung can resist serious infection for years. The usual history of these cases is that of recurring infection of the lung with periods of temporary improvement until finally lack of drainage leads to the complete picture of suppurative disease of the bronchi and lungs with constant cough and profuse expectoration often mixed with blood. It has long been noted that following even a relatively short period of obstruction by a benign neoplasm, the bronchi in the affected lobe show a marked degree of dilatation. Clubbing of the fingers at this stage of the disease is usually present. In isolated cases anaërobic infection is engrafted on the existing disease so that the clinical picture becomes one of lung gangrene and necrotic cavities originating from dilated bronchi are found in the lungs at autopsy (Case 13).

SPECIAL SYMPTOMS. *Age.* It will be noted that two-thirds of benign tumors of the bronchus occurred before the age of 40 years. In view of the similarity of this disease to malignant tumors of the bronchi and lungs, this fact becomes of some importance in differential diagnosis, as most cases of carcinoma occur after the age of 40.

Dyspnea. A unique form of dyspnea which may be very extreme due to change of posture of the patient is especially worthy of comment and may be regarded as pathognomonic of benign tumor of the bronchus. This occurred in Case 9. The patient observed that on changing to the recumbent position, his dyspnea became alarming. This is obviously due to the ball valve action of a pedunculated tumor which is displaced from its bronchus and obstructs the trachea.

Partial occlusion of a bronchus may also produce a whistling or sonorous sound during respiration, which may be more or less constant and to some degree localized over the affected lobe. In Case 17 this adventitious sound disappeared when complete occlusion of the bronchus occurred.

Hemoptysis. There is 1 symptom of benign tumor of the bronchus which is so outstanding that it deserves detailed consideration. In fact, it is the one symptom which is characteristic of this disease and is referable to the tumor itself, rather than to its pulmonary complications. This symptom is hemoptysis.

In the first place, recurring hemorrhage may be the only symptom for years before bronchial obstruction becomes manifest. Even

cough may be absent at this period of latency of the growth and it seems probable that the benign tumor may produce considerable narrowing of the bronchus without any cough resulting, providing infection of the lung has not yet taken place.

Hemoptysis occurred as a more or less prominent feature in 10 of our cases. It was commonly small in amount but in a number of the patients was profuse. One patient bled every month in such large amounts that she was almost exsanguinated and required a number of transfusions. In 2 patients the bleeding occurred only at the menstrual period. If careful inquiry were made it would probably be found that hemoptysis is the initial symptom in a considerable percentage of the cases.

There are certain features of the bleeding which distinguish it from hemorrhage due to other causes in the chest. The hemoptysis is very apt to occur suddenly without any warning and unassociated with other symptoms of pulmonary or bronchial disease. What is more striking is that the bleeding may cease just as abruptly without any subsequent period of streaking or staining of the sputum as is commonly the case when blood is derived from actual disease of the lungs.

One may explain this in the following way. Hemorrhage from benign tumors occurs in a main bronchus and the blood exudes from very small submucous vascular spaces. It is probable that bleeding of this character is slow and that the blood is expectorated before it can pass down into the smaller bronchi. This is further prevented by the presence of the occluding tumor below the point of bleeding. All of the blood is therefore promptly expectorated and little or none is aspirated into the smaller tubes. With a more brisk hemorrhage however, especially where there is not yet a bronchial occlusion, it is of course possible for the blood to be aspirated and to undergo the chemical changes which result in expectoration of dark blood for some days. It is therefore characteristic of bleeding from an occluding benign tumor that the hemorrhage is unexpected in its onset and, whether mild or severe, is apt to be equally sudden in its cessation and it is not succeeded by a period during which dark or otherwise altered blood is brought up. In this respect the bleeding differs from that seen in actual disease of the lungs or the hemorrhage from a malignant new growth or from varices in the bronchus.

In the stage of bronchial occlusion with pulmonary infection the expectorated blood may be either pure or mixed with mucus and pus.

Roentgen Examination. The roentgen examination plays an important though indirect rôle in the diagnosis of benign tumors of the bronchi. The tumor of course is itself invisible on the roentgen films. It is only when it is sufficiently large to cause an occlusion of a main bronchus that any changes can be observed on the roentgen film. At first this consists of an area of atelectasis in the lung.

This is usually lobar in distribution except in the occasional instances when the main bronchus is obstructed. Under these circumstances a whole lung will appear cloudy. The shadow of a collapsed lobe is fairly characteristic. If the collapse occurs in a lower lobe, especially on the left side, it may be associated with an elevation of the diaphragm which may obscure the shadow of the airless lobe.

When infection has supervened the roentgen appearance differs in nowise from that in cases of chronic pneumonitis with bronchial dilatation or lung abscess. In this late stage of the disease the affected side of the chest is collapsed, the lung or a part of it shows a dense infiltration and the heart and mediastinum are drawn over to the diseased side. Unless the clinical history is available the roentgen appearance affords no basis for a diagnosis of bronchial tumor and one is at a loss to distinguish between chronic inflammatory disease of the lung, malignant new growth, advanced unilateral tuberculosis and finally, benign tumor of the bronchus.

Bronchoscopy. The definitive diagnosis of benign tumor of the bronchus rests with the bronchoscopic examination. Everything that has gone before may be suggestive or strongly presumptive but only the bronchoscopic demonstration of the tumor furnishes a certain diagnosis. Invariably the bronchoscope discloses a smooth globular or oval tumor which may be sessile or attached by a pedicle and may thus be freely movable. In our series of cases the tumors had the following situations:

	Cases.
Right upper bronchus	1
Right middle bronchus	2
Right lower bronchus	6
Right main bronchus	1
Left upper bronchus	1
Left lower bronchus	4
Left main bronchus	2

Pathologic Changes in the Lungs. The severity of the pathologic changes in the lungs bears a close relation to the duration of the bronchial occlusion. When, as in Case 11, the tumor caused no obstruction to the bronchus there were no changes in the lung. In the cases in which there was an occlusion of presumably short duration, simple atelectasis of a lobe was present associated with retention of bronchial secretion. This was found in 4 cases (Cases 2, 4, 5, 10). In those patients in whom the disease had existed for longer periods, bronchiectasis and infection and induration of the lung with their pleural complications had occurred.

Duration. The exact duration of this disease is difficult to estimate because of the uncertainty of the time of its onset. The period of latency is variable and may be relatively long, as is evidenced by the patients in whom there were repeated hemoptyses for years. If bronchial bleeding or symptoms of pulmonary infection

are taken as presumptive evidence of a benign tumor we must conclude that the duration of the disease varies from months to years. The shortest history was 5 months and the longest 30 years. In the majority of cases symptoms pointing to the existence of a tumor were present for several years.

DIAGNOSIS. *Clinical.* The diagnosis of benign tumor of the bronchus presents 2 problems, first the recognition of this condition in the stage before bronchial obstruction, and second, in the stage of bronchial occlusion.

The Unobstructive Stage. Diagnosis at this time is more important as permanent damage to the lung has not yet occurred and removal of the tumor may result in a complete cure. However, the diagnosis is more difficult because the physical and roentgen examinations are negative. A tumor should be suspected when there are recurring bleedings from the bronchus which have the characteristics previously described. Such bleeding should at once invite bronchoscopy.

The Obstructive Stage. The diagnosis is of practical importance because the removal of the tumor may prevent the infection of a lung which is already collapsed; it may also cure a suppurative bronchitis and may even cause a pneumonitis to subside. However, in the longstanding cases when bronchial dilatation has occurred or actual suppuration of the lung is present, removal of the tumor will not lead to permanent improvement. The diagnosis rests upon a suggestive history of recurrent bleeding supported by the physical findings of obstruction of a bronchus and evidence of suppurative disease of the bronchi and the lungs. These latter findings are usually demonstrated by the roentgen film. Here again, the bronchoscope brings the only certain proof of the existence of a benign tumor.

Microscopic. We have already described the microscopic characteristics of adenomatous polypi of the bronchus. It is however, worthwhile to emphasize the errors in diagnosis which are likely to occur in the interpretation of the minute pathology of material removed through the bronchoscope. It has happened in several of our cases that tissue removed has been regarded by the pathologist who did not know the clinical features of the case, as carcinomatous. In Cases 4 and 16, for example, the microscopic report was carcinoma and endothelioma, although the condition had existed for 4 and 7 years respectively without any evidence of invasion of the lung. In Case 16 a diagnosis of endothelioma had been made 7 years before. Recently a recurrence of the symptoms afforded an opportunity for another microscopic examination which showed a typical adenomatous polyp. In such cases therefore, especially where the youth of the patient and the long duration of the symptoms indicate the probability of a benign tumor, the microscopic findings must be subjected to a critical appraisal.

PROGNOSIS. The prognosis of this disease follows from the preceding observations. It is closely related to the time when the diagnosis is made and depends entirely upon the removal of the tumor before permanent damage has been done to the bronchi and lungs. In 6 of our cases it was possible to remove the tumor and more or less completely relieve the patients of their symptoms, which have not recurred. In 1 case the tumor was removed after 4 years. There has been a tendency for the persistence of atelectasis of lobes which have been collapsed for some time. This apparently is tolerated with few or no symptoms providing the bronchus is patent. In 4 cases owing to the long duration of the disease with consequent permanent damage to the lungs there has been a persistence of the symptoms in spite of partial or complete removal of the tumor through the bronchoscope. In 1 case (Case 11), the diagnosis was made in the pre-obstructive stage because of bleeding. This tumor was so recently removed that nothing can yet be said of the final outcome. Two patients (Cases 7 and 13), died as the result of an empyema which was secondary to advanced suppurative disease of the lung. The diagnosis of bronchial tumor was only made postmortem. Two cases (Cases 15 and 14) died, 1 after an operation for lung abscess and the other of a putrid empyema. Both showed extensive bronchopulmonary disease. The last 2 cases (Cases 16 and 17), which have come under observation recently are still under treatment. Although the tumors are being removed, the final outcome is in doubt because of extensive changes which have occurred in the lower lobes due to occlusion of the bronchus. It is not improbable that if drainage through the bronchus can be established the patients may have a symptomatic cure.

TREATMENT. The treatment of benign tumor of the bronchus consists in the removal through the bronchoscope of the obstructing tumor. Details of this treatment are discussed by Kramer in a recent publication[3] to which the reader is referred. The complete removal of the tumor at once may not be possible. There is further a tendency in some cases for the growth to recur after an interval of years. In Case 16 this interval was 4 years, during which the patient remained in perfect health. The pulmonary complications of this disease may require surgical treatment such as the drainage of empyemas or suppurative foci in the lung. It should be especially noted that in cases of empyema of obscure origin, the possibility of an obstructing tumor of the bronchus should always be considered when there is persistent discharge of a sinus.

We append a short history of our 17 cases:

CASE 1.—S. S., aged 28 years. Male. September, 1920.

History. "Grippe" 1 year ago. Pneumonia with left pleurisy 8 months ago. Since then constant cough with expectoration and dyspnea on exertion. Eight weeks ago a recurrence of left pneumonia; for 3 weeks daily chills and fever.

Examination. Left chest smaller; left lung posteriorly dullness with absent breathing over lower lobe. Clubbing of the fingers. Chest aspirative negative. Temperature continued daily up to 104° F. until November, when bronchoscopy was performed. Two centimeters from bifurcation the lumen of the left bronchus was closed by a smooth, round mass covered by normal mucosa. It was attached to the outer wall above the opening of the upper branch and filled the lumen of the main bronchus almost completely. Pus issued from behind the tumor. After removal of the tumor the patient made a complete recovery, so that by December 22 all shadows had disappeared from the Roentgen film. The latter had previously shown a dense shadow of inflamed, collapsed lung with displacement of the mediastinum to the left.

CASE 2.—A. De G., aged 36 years. Female. February, 1929.

History. Right-sided pleurisy with effusion 13 years ago. Was ill for 3 months with fever. Nine years ago had "grippe" which was repeated three times since. One year ago there was a gush of 3 ounces of bright red blood from the mouth. This was at the time of her menstrual period. Since then she had two similar attacks, also at her menstrual period. Bleeding began and stopped abruptly. During this time the patient had frequent colds with pains in her right chest on breathing.

Examination. Signs of an infiltration over the right middle lobe with atelectasis. Thickening of the pleura at the right base.

Bronchoscopy: Showed a round mass covered with mucous membrane in the right middle bronchus, entirely occluding it. Specimen removed showed microscopically adenoma. After complete removal of the tumor patient remained well.

CASE 3.—N. MacQ., aged 17 years. Female. December 25, 1925.

History. During the previous 5 years she had frequent hemoptyses (perhaps 100) of 1 to 5 ounces of blood. These were at first more severe in the winter time when she had a severe cough. Since then they also occured in the summer. They usually occurred at the menstrual period. Frequent nightsweats. Two months ago she had fever for 2 days and was told she had pneumonia. For 2 weeks patient felt warm in the afternoon. No loss of weight.

Examination. Patient well nourished and did not look ill. The whole right lower lobe was flat, with distant breath sounds and absent fremitus. Clubbing of fingers.

Bronchoscopy: Showed a tumor occluding the right lower bronchus, which bled easily. Microscopic examination showed an adenoma. Tumor could not be removed because manipulation caused alarming hemorrhage.

Patient was observed for 3 months, during which she had profuse large hemorrhages and periods of high fever. The signs in the lung were due to atelectasis and infection. Patient was not improved.

CASE 4.—J. P., aged 26 years. Male. August, 1926.

History. Began 3 years ago with pneumonia and pleurisy with effusion on left side. Then developed a cough with hardly any sputum. Two years ago he went to Colorado as a tuberculosis suspect because of hemoptyses. During the last 2 years he has had several fairly large hemoptyses. In Colorado he was declared nontuberculous. For the last 8 months cough was more persistent with dyspnea on exertion. No fever.

Examination. Signs of complete closure of the left lower bronchus. A loud rhoncus over the left lung. Roentgen examination showed collapse of left lower lobe with an elevation of the left diaphragm.

Bronchoscopy: Showed an adenomatous tumor at the origin of the left lower bronchus which completely filled it.

Subsequent Course. Patient was so much improved by bronchoscopy that he refused further treatment to remove the tumor. He remained

well until 1927, when he had a recurrence of his bleeding. In February he had an acute pneumonia with high fever, which subsided promptly after the removal of some tumor tissues through the bronchoscope. On March 23 three radium seeds were inserted in the bronchial wall at the site of the tumor.

Since then the patient has been free of cough or any other symptoms. Roentgen examination still shows some collapse of the left lower lobe, which is, however, gradually expanding.

CASE 5.—M. D., aged 38 years. Male. January, 1929.

History. Pneumonia 9 months before, with high fever and right pleural pain. This was followed by cough and blood-stained sputum for several weeks. Since then constant pain in the right chest anteriorly. Cough with no expectoration. Roentgen examination showed a shadow in right middle lobe due to atelectasis. Lung abscess had been diagnosed and a phrenicotomy performed.

Bronchoscopy: January, 1929. Showed middle lobe bronchus occluded by a gray lobulated tumor, 5 by 9 by 12 mm. This was removed with forceps. Microscopic examination showed an inflammatory polyp.

Subsequent Course. For some time the patient had a persistence of his pain. Repeated bronchoscopy for the removal of small recurrent polypoid masses. He is now well.

CASE 6.—J. F., aged 48 years. Male. March, 1929.

History. In 1917 the patient had "grippe" and pneumonia and was sick in bed 19 weeks. For 3 to 4 years he had slight burning pain in left upper chest. One and a half years ago he began to cough and continued to cough with greater frequency and increasing expectoration. This continued for 6 months, with increasing cough and so much dyspnea that he was told he had asthma. This became so severe that he could not lie down at night. One year ago the patient began to spit blood for 2 or 3 days at a time. This would begin abruptly. This continued to the present time.

Examination. Showed an infiltration in the mesial part of the left lower lobe. Marked clubbing of the fingers.

Bronchoscopy: Examination showed a pedunculated tumor in the left lower lobe. Following the removal of this tumor the patient made a rapid recovery.

CASE 7.—B. W., aged 47 years. Female. June, 1927.

History. The patient had pleurisy 5 years before admission and empyema 2 years later, for which thoracotomy was performed on the right side. A persistent sinus remained to the present time. Cough which had been present for at least 3 years continued with moderate amount of blood-streaked sputum. A diagnosis of lung abscess was made, for which a collapse operation had been performed in April. In June the sinus was injected to determine a communication with the bronchus which could not be demonstrated. In July, in an attempt to split open the sinus for better drainage, the patient bled to death through the fistula. Among other clinical findings the blood and urine showed signs of a nephrosis, resulting from the long-continued suppuration.

Autopsy. In the left lower lobe bronchus there was found a freely movable cylindrical pedunculated tumor, 21 by 6 mm. The bronchus distally was markedly dilated and opened into a cavity leading into a sinus to the chest wall. There were numerous sacculated dilatations filled with blood. The hemorrhage had come from a dilated branch of the pulmonary artery in the wall of one of the sacculations.

The tumor was composed of glandular structures, separated by thin connective tissue septa. It was an adenomatous polyp.

CASE 8.—J. K., aged 27 years. Female. September 20, 1929.

History. Eleven years ago the patient had influenza followed by pneumonia and pleurisy. Since then she had more or less constant cough. A few

times a year sputum was slightly bloody. She had many colds. One year ago she began to have slight dyspnea on exertion. Three months ago pain in the left chest with a great increase in the frequency of cough. Constant fever up to 101° and much loss of weight.

Examination. Chronically ill woman with a harrassing cough, with thick, blood-streaked sputum. Trachea displaced to the left. The volume of the left chest smaller than the right and moved less in respiration. Dullness in the upper part of the left lung increasing to flatness at the base. The breathing sounds in the upper lobe distant and absent at the base. Heart displaced to the left side. Slight clubbing of the fingers. Daily temperature from 101° to 102°.

Bronchoscopy: Trachea displaced to the left side. Complete obstruction of the main bronchus by a globular tumor mass, which bled profusely. This mass was situated 2 cc. from the bifurcation.

Microscopic examination: Adenoma. Patient refused further treatment and remains unimproved.

CASE 9.—I. L., aged 64 years. Male. September, 1926.

History. Cough for 30 years, with hemoptysis 4 to 5 times a year for 30 years. Five years, shortness of breath and substernal oppression. For 3 months precordial pain radiating down the left arm. Weakness, loss of 36 pounds and increasing dyspnea. Pain less on walking, becoming worse on lying down.

Examination. The patient was poorly nourished. Profuse purulent expectoration. Lungs, dullness over the left upper lobe. Marked clubbing of the fingers.

Bronchoscopic examination: There was a flat tumor in the left main bronchus near the orifice of the upper lobe branch. This tumor was covered with normal mucous membrane and moved to and fro. It partly obstructed the left upper lobe bronchus.

Roentgen examination showed a fibrotic infiltration in the left upper lobe.

Tumor was not removed and patient was unimproved.

The interesting feature of this case was the unusual type of dyspnea on changing to the recumbent position, which was evidently due to the upward displacement of the pedunculated tumor causing an obstruction of the trachea.

CASE 10. D. M., aged 36 years. Male. February, 1930.

History. Five months before admission the patient had a cough and coryza. Cough gradually became productive of small amounts of whitish sputum. On 6 occasions in the last 3 or 4 months he spat up 2 to 3 drams of blood preceded by a peculiar sensation under the sternum which disappeared after the blood was expectorated. Six months before admission he had his tonsils removed.

Examination. Well-nourished man. Signs of pneumonic infiltration over the right lower lobe, with a few râles and diminished breathing.

Bronchoscopy: Showed an irregular stenosis of the right lower lobe bronchus, which bled freely. Tissue removed was found to be an inflamed polyp. Patient was repeatedly bronchoscoped and bronchus dilated after removal of more polypoid tissue with gradual improvement of the symptoms. When last seen aëration of the right lower lobe had improved and, although bronchoscopy showed a cicatrical narrowing of the right lower lobe bronchus, patient was symptomatically well.

CASE 11.—I. B., aged 54 years. Female. October, 1930.

History. Twenty years ago the patient had a heavy cold with small hemoptysis. Sputum negative and not considered a case of tuberculosis. Three years ago she began to cough and coughed each winter, bringing up blood on 5 or 6 occasions. Amount of blood expectorated was ¼ cupful, lasting for 1 to 2 days, followed by streaking for 1 to 2 weeks. Three weeks before she had 2 hemoptyses.

Examination. Healthy looking woman with no signs of pulmonary disease. Roentgen examination of chest was normal.

Bronchoscopy: In posterior wall of left main bronchus just above lower lobe branch was a soft, small mass, which bled easily.

Microscopic examination: Although the gross appearance and the clinical history indicate definitely that this is a benign tumor, the microscopic examination shows some infiltration of the stroma which the pathologist would regard as suspicious of malignancy. This is one of the cases in which the pathologic data must be accepted with much reservation and the clinical facts should take precedence in the diagnosis.

CASE 12.—K. M., aged 44 years. Female. May, 1922.

History. Began with upper respiratory infection 6 months before with productive cough which became more and more severe. Sputum was gray and contained no blood.

Examination. Well-nourished woman. Constant dry cough. Lungs showed dullness with diminished voice and breath sounds over the right lower lobe. Marked clubbing of the fingers.

Roentgen examination showed a dense pneumonic infiltration of the right lower lobe.

Bronchoscopy: Three centimeters below the bifurcation the right bronchus was completely closed by a tumor. The tumor was covered with granular mucous membrane and had a benign appearance.

Microscopic examination: Showed adenoma.

CASE 13. D. L., aged 32 years. Female. October, 1919.

History. One and a half years ago pleurisy on the right side. Since then apparently well. Two weeks before she began to cough and brought up small amounts of purulent sputum. Following this, temperature arose to 102° F. She had some dyspnea.

Examination. Well-nourished woman. Acutely ill with dyspnea and cyanosis. Signs of an effusion in the right chest associated with pneumonia.

Roentgen examination showed a consolidation of the lung with multiple cavities and pleural effusion.

Thoracotomy performed for empyema and large amount of pus evacuated. Before she died, two days later, she expectorated foul purulent sputum.

Autopsy. There was an abscess cavity in the right lower lobe. In the wall of the right main bronchus projecting into the lumen there was a mass the size of a cherry, which almost completely occluded it. The bronchi distal to the mass were dilated.

Microscopic examination: Showed the tumor to be a lymphoma.

CASE 14.—C. S., aged 48 years. Male. April, 1913.

History. Onset 2 weeks before with cough, fever and pain in left lower chest. Little sputum.

Examination. Patient acutely ill with temperature 103° F. Dyspnea and severe cough. Signs of a pyopneumothorax on the left side. Patient died suddenly after operation.

Autopsy. Showed in the left lower lobe bronchus a cauliflower tumor, 2 cm. in diameter. The tumor was firm, not ulcerated and extended into the bronchial wall at its base for about 3 mm. No invasion of the peribronchial tissue.

Microscopic examination: Showed the tumor to be an adenoma.

Apparently the bronchial stenosis had resulted in pulmonary infection, with a secondary anaërobic infection of the pleura.

Comment. Although the duration of the symptoms is given as 2 weeks, this must be doubted.

CASE 15.—J. M., aged 35 years. Male. January, 1915.

History. A detailed history was not obtained. It was known, however, that the patient had been coughing and bringing up large amounts of

purulent sputum every day, as much as 5 ounces. This had occurred for a considerable time. A diagnosis of lung abscess was made and patient operated upon. He died suddenly during aspiration of the lung.

Autopsy. Showed a chronic pneumonitis of the right lung with universal extreme dilatation of all the bronchi. There was an abscess in the pleura between the middle and lower lobe which communicated with the middle lobe bronchus. In the right lower lobe bronchus there was a tumor, 2.5 cm. in diameter, situated 4 cm. from its origin. The tumor was smooth and firm.

Microscopic examination: Showed adenoma.

CASE 16.—J. L., aged 32 years. Male. December, 1929.

History. Onset 7 years before, with attack of "grippe" with fever and dry cough. Continued to have fever for 1 year with dry cough. In May, 1925, he was bronchoscoped and a tumor found in right lower bronchus. The tumor was microscopically diagnosed as endothelioma. During the next year he had hemoptyses every 4 months of 1 to 2 cupfuls of bright red blood. He was then given a course of 12 treatments with the Roentgen ray over the tumor. Following this for nearly 4 years he remained well without cough or expectoration.

Two nights before admission to the hospital he brought up several tablespoonfuls of bright red blood. Bleeding became more active and on admission he brought up 1½ cupfuls of bright red blood with clots.

Examination. Patient was well nourished. Bleeding actively from his bronchus. Lungs: Dullness, diminished breathing, voice and breath sounds in the right lower lobe. No clubbing of the fingers.

Bronchoscopy: Showed a mass growing from the spur of the right main bronchus, blocking the right lower lobe branch. The mass was smooth and covered with a vascular mucous membrane.

Microscopic report: Adenoma. It is obvious that the previous diagnosis of malignant growth of the bronchus was incorrect. The adenoma is now being removed by electrocautery through the bronchoscope. The right lower lobe is collapsed and probably indurated.

CASE 17.—H. F., aged 35 years. Female. January, 1931.

History. Two years ago the patient had a sensation of pressure over the right lower chest anteriorly. From then until 4 months ago she felt in good health, but was aware, more or less constantly, of a whistling noise in her chest which she attributed to asthma, although she had no shortness of breath. Four months ago she got a sudden pain in her right chest, with fever and a dry cough. These symptoms have continued to the present time, with the addition of a small hemoptysis recently. She had no expectoration.

Examination. Well-nourished woman. Daily temperature up to 101° F. Marked clubbing of the fingers. Lungs: Dullness over the right lower lobe with much diminished breathing. A loud rhoncus is heard over the entire right chest which is more or less constant.

Roentgen examination: Showed an infiltration of the right lower lobe with numerous bronchial dilatations of large size.

Bronchoscopy: Showed a tumor completely occluding the right lower bronchus which on microscopic examination proved to be an adenoma.

The history of this case indicates that there was a tumor in the right lower lobe bronchus for at least 2 years, with probably atelectasis of the right lower lobe. The active symptoms of the disease began 4 months before with an infection of the lung which has since continued.

We wish in conclusion to record some observations which appear to indicate that a benign tumor of the bronchus may undergo a

transformation into a carcinoma with invasion of the lung. In the following 2 cases, the clinical course of the disease and the pathologic findings indicate that this was probably the sequence of events.

CASE 18.—E. F., aged 33 years. Female.

The clinical symptoms began in April, 1921, with cough and expectoration of a small amount of blood. After 4 months of quiescence the same symptoms recurred, together with some fever and dyspnea. Patient was then well for 6 months, when her cough returned. When first examined, in April, 1922, she had lost 33 pounds. She presented on physical examination an atelectasis of the left upper lobe. The bronchoscopic examination showed a compression of the left lower lobe from which creamy pus issued, but no tumor was seen. The patient lived until the early part of 1929 with symptoms of suppuration of the lungs, when she finally died. At autopsy, a polypoid tumor was found obstructing the left main bronchus, with a secondary suppurative disease of the left lung with multiple cavities. Microscopic examination showed carcinoma.

We have here a case which lasted for 8 years and showed at autopsy a malignant tumor of the bronchus. It is not likely that a carcinoma of the lung could have existed all this time. The polypoid appearance of the tumor (Fig. 4) and the long history of proven stenosis of the bronchus with pulmonary infection can lead to no other conclusion than that originally and for a number of years therafter the tumor was a benign adenoma, and only latterly did it undergo a malignant degeneration at its base.

The next case, though of shorter duration warrants the same conclusion in regard to the pathogenesis of the tumor.

CASE 19.—H. S., aged 33 years. Male. February, 1928.

History. Patient had cough every winter for a number of years, with occasional spitting of blood. Two months previously he caught cold with an increase of his cough and some fever. He had pain in his right chest for 3 weeks with spitting of bloody sputum.

Examination: The patient was acutely ill with fever. Physical examination showed a pleural effusion occupying the lower two-thirds of the right chest. There was some clubbing of the fingers.

Bronchoscopic examination: Showed a bilobed round mass in the right main bronchus near the upper lobe branch covered with normal mucous membrane and dilated vessels. In the lower part of the main bronchus there was an irregular granular mass. This proved microscopically to be a carcinoma originating from the submucous glands. The patient later died of pulmonary hemorrhage.

In this case the history of cough with spitting of blood for a number of years makes it likely that the smooth polypoid tumor which was seen in the bronchus had probably been benign and had existed for some time and that only recently it became malignant. This is further borne out on the roentgen film by the absence of any infiltration of the tumor into the lung.

Our experience in these 2 cases, in which a carcinoma developed from a preëxisting benign polypoid growth, is an added reason for the prompt removal of these tumors.

Summary. Based on a study of 17 cases, we have sought to define a clinical picture of benign tumors of the bronchus. Our study has been concerned mainly with that form of tumor known as adenoma, which appears to be the commonest type encountered clinically. The following facts are emphasized.

1. Care must be exercised in the microscopic diagnosis of these tumors lest they be mistakenly regarded as malignant.

2. Benign tumors o the bronchus probably have a long period of latency during which there may be no symptoms of bronchial obstruction or bronchial irritation.

3. In a considerable percentage of the cases th s period is characterized by repeated hemorrhages.

4. Aside from the symptoms of bronchial obstruction and infection, pulmonary hemorrhage is a frequent symptom of adenoma of the bronchus. This bleeding has certain characteristics which may suggest the diagnosis.

5. When stenosis of a bronchus with infection of a lung has occurred the clinical picture may be confusing. These clinical pictures are described.

6. The prognosis of benign tumors of the bronchus depends upon the early discovery and removal of the tumor, which may lead to prompt cure. When secondary inflammatory changes have occurred in the lung, the outlook is not good.

7. Evidence is adduced which indicates that polypoid adenomas may undergo malignant degeneration.

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THE FREQUENT OCCURRENCE OF ABNORMAL CUTANEOUS CAPILLARIES IN CONSTITUTIONAL NEURASTHENIC STATES.

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In 1912 Lombard described a simple method for direct microscopic examination of the minute vessels of the human skin. He rendered the superficial epithelium transparent by applying gly-

FIG. 1.—Normal capillaries in a man aged 40 years. The hairpin form predominates.

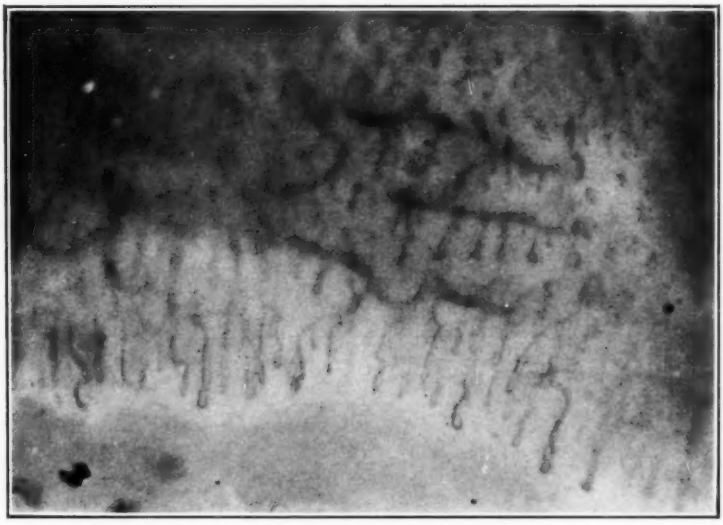

FIG. 2.—Capillaries in a man, aged 65 years, with marked arteriosclerosis. Corkscrew forms are frequent. The subpapillary venous plexus shows with unusual distinctness.

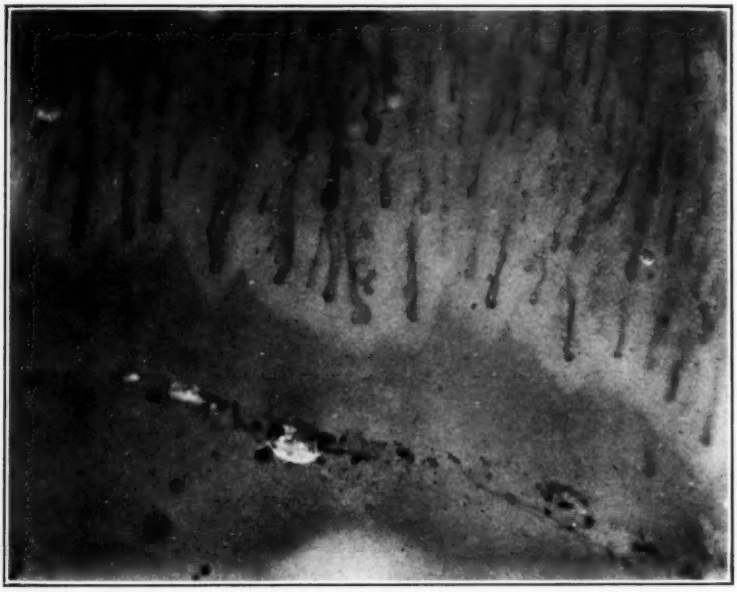

FIG. 3.—Capillaries of Case 1, showing abnormally shaped forms. Note the intricate pattern of the central capillaries.

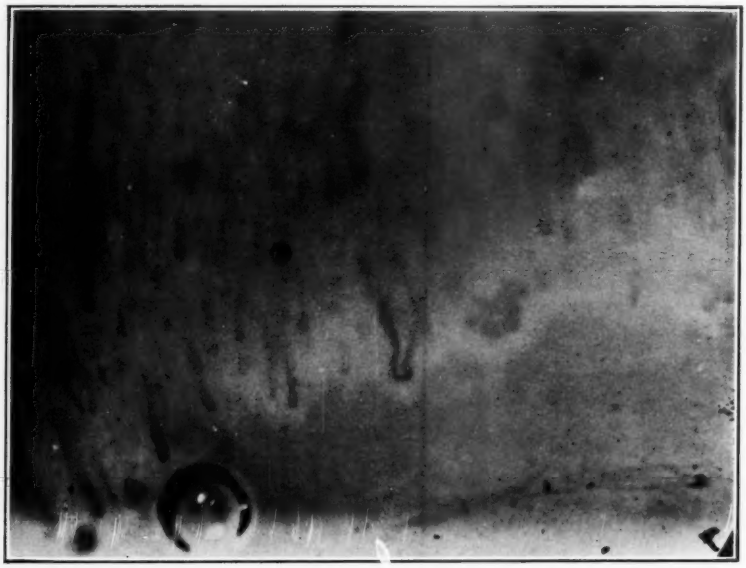

FIG. 4.—Capillaries of Case 2, showing one large straight loop, and one netlike formation.

cerin or cedar oil, and inspected the skin directly through the microscope, using a strong, oblique light. The skin just back of the nail was found most suitable for observation, for there the capillaries course more nearly parallel with the skin surface, and are, therefore, visible through most of their extent. Ordinarily they are hairpin shaped, of fairly uniform size and arranged in parallel rows, connecting the subpapillary venous and arterial plexuses. The subpapillary venous plexus is superficial to the arterial, and is frequently visible. Brown[5] gives the average visible length of the capillary loop as 0.42 mm., with a width of 0.007 mm. for the arterial and 0.009 mm. for the venous limb. Frequently loops are rotated, constituting the corkscrew forms. Since Lombard's work many reports have been published describing capillary changes considered characteristic of many diverse conditions, including Raynaud's disease, acrocyanosis, scleroderma, erythromelalgia, arteriosclerosis, nephritis, primary and severe secondary anemias, purpura, diabetes, polycythemia, certain neurasthenic states, and certain cases of idiocy.

The engorgement and widening of the vessels in polycythemia vera was well shown by Brown and Giffin.[3,6]. The converse, the thinning of the caliber in severe anemias, is also generally accepted. Probably the most exhaustive capillary studies were those made by Ottfried Muller with his associates, E. Weiss, Niekau, and Parrisius. He describes dilated fantastically coursing capillary forms with an intermittent type of bloodflow in Raynaud's disease, erythromelalgia, acrocyanosis, and in certain neurasthenic states that he terms the "vasoneurotic diathesis." In acrocyanosis the intermittency of flow is least marked, and there is definite capillary dilatation, especially on the venous side. Brown[5] in studying a series of cases of Raynaud's disease, described periods of interference with capillary bloodflow during typical attacks, believed due to spasm in the arterial system. Brown and O'Leary[4] report two capillary pictures in scleroderma; the one identical with Raynaud's disease and followed they believe by secondary scleroderma; the other with huge dilated atonic capillary loops, even large enough to be visible macroscopically at times, associated with primary scleroderma. In diabetes, Muller and his associates have described a thickening of the midportion of the capillary loop, at the junction of the arterial and venous limbs, but this is denied by most observers. The German investigators have seen minute capillary hemorrhages visible only microscopically in purpura. Powdermaker, reviewing the work of Hoepfner, Jaensch, Wittneben, Weygandt and Kahle, and adding some observations of her own, describes an abnormal capillary picture in congenital idiots, especially common in those with associated physical maldevelopment, which she believes to be due to persistence of fetal and infantile forms. In nephritis, E. Weiss says the number of capillary loops is increased, and the individual vessels

are longer and wider than usual, and are greatly looped. This finding has not been confirmed by others.

Under the term "vasoneurotic diathesis" Muller describes a syndrome with a clinical and a capillary part. Patients with this condition may have any of the symptoms or symptom complexes which ordinarily lead to the diagnosis of neurasthenia or psychasthenia. They are persons who have belonged to this category since early childhood, and are totally unable to cope with an even moderately exacting environment. Emotionalism and a subjective and objective vasomotor instability are prominent symptoms. They are said to weep and blush easily, and their hands are cold and clammy most of the time, especially under stress. Their capillaries are disordered in arrangement, variable in size, but, most pathognomonic of all, show fantastically coursing and frequently large forms. The intermittency of the flow is not so marked as in Raynaud's disease, and the widening of the diameter is not so great as in Raynaud's disease, erythromelalgia, or acrocyanosis. However, the differential diagnosis from the organic vascular disturbances just mentioned can best be made by the clinical history. L. A. Miller[8] mentions the condition and states that he has seen 3 such cases which he does not report in detail.

In this investigation some 600 cases were studied, including patients in the wards and the outpatient departments of the University Hospital. These patients presented a great variety of clinical conditions. For the purpose of this paper, patients with obvious peripheral vascular disease or engorgement, including acrocyanosis, Raynaud's disease, polycythemia and scleroderma are excluded.

Over 500 cases were studied that showed no evidence of organic peripheral vascular lesions, other than perhaps a sclerosis commensurate with age. In 31 of these cases the diagnosis included a functional "neurasthenic" condition. Of these 500 cases, 8 cases showed a definite morphologically abnormal capillary picture. By that is meant that a considerable number of the capillaries viewed in practically any field are abnormal. The clinical diagnoses were interesting. Two were diagnosed simply as psychoneurosis; 1 as psychasthenia; 2 as neurocirculatory asthenia; 1 as neurasthenia and hyperthyroidism (?), the (?) because the basal metabolism was normal though there was a slight goiter; 1 as vasomotor neurosis and essential hypertension; and 1 as infectious arthritis and infected tonsils. This last case (No. 1 in the case histories) alone did not have a functional diagnosis, even in part, though from the records it is fairly obvious that one could easily have been made. It will thus be seen that all 8 cases are included in the 31 with a functional diagnosis in whole or in part. These cases, as will be shown later, fall fairly well into the clinical syndrome described by Muller. However, it is also to be noted that 23 cases with similar diagnoses had perfectly normal capillary pictures.

Method. The light from a 500-watt lamp is cooled by passing through a spherical liter flask of water and concentrated by a single planoconvex lens to fall upon the stage of an ordinary microscope at an angle of about 45°. A 7.5 ocular and a 32 objective were found most suitable for observation and for photography. For observation the unprepared skin of the finger just back of the nail was covered with cedar oil and examined on the stage of the microscope supported only by the grasp of the examiner. For photography the finger was placed in a small wooden box gently but firmly supported with plasticine, the arm resting on pillows, and the box strapped with adhesive to the stage of the microscope. In addition, a fragment of a cover glass was usually placed on the cedar oil to prevent bubbles in the field. The capillary circulation in the area to be photographed was observed before and after this manipulation, and in no case reported did any obvious change occur. Though an attempt was made to choose a representative field, it was usually necessary to select the area opposite the middle of the nail which is in general the flattest area and where the greatest number of loops appear in a single focus. For technical reasons, considering the support of the hand on the stage, the ring finger was found to be the most convenient. Photographs were made using a Leitz camera, style Maccam, taking Wratten and Wainwright panchromatic plates, size $3\frac{1}{4}$ by $4\frac{1}{4}$ inches. An exposure of one second was required.

In the following case reports, all fingers of both hands were examined and the ring finger of the left hand photographed. All photographs are untouched. Magnification is × 32, *i.e.*, 1 mm. on the finger equals 32 mm. on the plate. Although these photographs are far from being technically perfect, it should be noted that they are untouched and at least as good as others of their kind. They should not be compared with drawings of capillary loops or "touched up" photographs.

Material. Figs. 1 and 2 illustrate normal cases. The first is of a man aged 40 years. His loops are overwhelmingly of the hairpin type. The visibility is rather good, and more than the distal line of loops are clearly shown. Here and there a short section of the venous plexus is seen, but this is not nearly so obvious as in the second case, a sclerotic individual aged 65 years, in whom the broad streamed plexus is plainly visible at the base of the loops. This visibility or nonvisibility of the venous plexus is purely a matter of individual differences, but the increased tendency to corkscrew forms in the distal loops of the older man is usually considered typical of arteriosclerosis.

The first and second cases reported are illustrated in Figs. 3 and 4, while the last 6 cases are not illustrated.

Case Reports. CASE 1.—R. S., a young woman, aged 26 years, had been extremely nervous since childhood. Her hands would become icy

cold and tremble on the slightest provocation. This emotionalism had prevented her from getting along in school or from holding a position afterward. Eleven months before admission, during pregnancy, she first noticed some pain in both elbows, worse on motion. At times her fingers felt stiff. This condition continued in a rather mild form until admission. Physical examination was essentially negative, except for very slight limitation of motion in the joints above mentioned. Pulse rate was not elevated. Blood count, urinalysis, blood urea nitrogen, blood Wassermann, gynecologic consultation, cervical smear for gonococci, gonococcus complement fixation, chest Roentgen ray—all revealed nothing significant. Joint Roentgen ray showed a slight thinning of interarticular cartilages of both elbow joints, and possibly slight periarticular thickening about certain interphalangeal joints, but no bony change anywhere. Tonsils were found to be diseased and were removed. Clinical diagnosis was infectious arthritis and infected tonsils.

During her stay in the ward she would weep when her bed was approached on ward rounds. Finally in an emotional outburst she left the hospital against advice. Fig. 3 shows the capillaries of this patient. The variation from the normal hairpin and corkscrew forms is striking. The demarcation between the corium and the epithelium shows with unusual clearness.

Case 2.—B. L., a woman, aged 35 years, came of what she described as a nervous family. From early childhood she had been emotionally unstable, subject to cold hands on the slightest provocation, and had been addicted to biting her nails. She had married and was leading a sheltered life in her home. Three years before admission she had begun to suffer with headaches and at times felt quite dizzy. It was found that she had high blood pressure. She was never incapacitated from her household duties which were, however, not heavy. During the 6 months in which she was followed in the ward and dispensary her systolic blood pressure remained at 200 or a little over, while the diastolic remained at 130 to 140. There was no definite sclerosis, except in the retina, where there was slight angiosclerosis reported. Blood count, urine, phenolsulphonephthalein kidney function test, blood urea nitrogen were all within normal limits. A diagnosis was made of essential hypertension and vasomotor neurosis. Her capillaries are pictured in Fig. 4. Note one large, fairly straight loop and a netlike formation beside it. The last formation, somewhat resembling a glomerulus, is difficult to photograph because its blood channels do not all lie in the same plane.

Case 3.—J. D., a man, aged 29 years, had always been extremely nervous, emotional and subject to cold hands and feet under slight emotional stress. Three years prior to admission he became definitely worse, with epigastric distress, belching, occasional palpitation and heart consciousness, general nervousness and irritability. He said that when his boss called him into the office he felt as though something had been turned off inside him. Diagnoses prior to admission had been psychoneurosis, hyperthyroidism.

The blood pressure was 126 systolic and 88 diastolic. Hemoglobin was 98 per cent and the red blood cell count 5,400,000.

He was somewhat underweight, but otherwise his general physical examination was negative. Examinations of his urine, blood sugar, blood urea nitrogen, basal metabolic rate, blood Wassermann, gastric analysis, Roentgen rays of heart, lungs and gastrointestinal tract and electrocardiogram all revealed nothing abnormal. Pulse varied between 110 and 62, averaging about 80. A diagnosis of psychoneurosis was made. Capillary examination showed a picture very similar to Fig. 3, except that there were also a considerable number of large, straight loops, as seen in Fig. 4.

Case 4.—M. M., a woman, aged 27 years, had never been in good health. She had been nervous, somewhat emotional, subject to cold hands and feet

under stress. However, she carried on fairly well until 3 years ago, when she noticed increasing nervousness, irritability, palpitation and loss of weight. She was diagnosed hyperthyroidism elsewhere without a basal metabolism test, and treated with Roentgen ray with transient benefit. Physical examination showed nervousness and slight thyroid enlargement. Basal metabolic rates, as outpatient, +10 and +22; in the hospital, +3. The pulse rate varied between 60 and 100, averaging about 80.

The blood pressure was 130 systolic and 90 diastolic. Hemoglobin was 75 per cent and red blood cell count, 4,200,000. A diagnosis of neurasthenia and hyperthyroidism (?) was made. Capillary examination showed a picture essentially similar to Fig. 3.

CASE 5.—F. W. S., a man, aged 27 years, had always been nervous. He would have palpitation on any emotional excitement, and his hands would get cold and tremble. This dated from childhood. In December, 1929, he developed a slight cough and seemed definitely worse. He was happy in his work, and had not been subjected to any additional emotional strain, except a sexual one. His wife had been pregnant twice. The first child lived only 4 days and a second child was stillborn. His wife had been told that a third pregnancy would seriously jeopardize her health. For the past year or two the patient had been living in dread that this might occur.

The blood pressure was 165 systolic and 105 diastolic. Hemoglobin was 102 per cent, and red blood cell count 5,300,000.

Physical examination showed a sclerosed left drum and a nasal septum deviated to the right. Examinations of the urine, basal metabolic rate, chest Roentgen ray, blood urea nitrogen, Wassermann and phenolphthalein test all revealed nothing abnormal. Sinus disease was found and sinus surgery begun. Pulse varied between 100 and 70 while in the ward, averaging close to the lower figure. A diagnosis of psychoneurosis was made. Essential hypertension was suggested but not definitely diagnosed, because of the systolic blood pressure of 165. Capillary examination showed a definitely abnormal picture very similar to Fig. 3.

CASE 6.—M. C., a woman, aged 33 years, had been sickly and emotional since childhood. Her hands and feet were almost constantly cold, especially under stress. Four years before the time of first examination she had been found to have diabetes and had been treated for it with diet and insulin, with excellent results. Her mental condition was markedly abnormal. She would at times have strong imperative impulses to cry out and make a scene. Again she would be weak with terror for fear two automobiles, though distant and going slowly, would collide. She was self-conscious in crowds, and imagined people were looking at and talking about her. She had worked at routine factory tasks at times, but left capriciously when she took a dislike to her position. She had no definite illusions or delusions, and her intelligence was fairly good. The psychiatric consultant made a diagnosis of psychasthenia.

Physical examination and blood count were essentially normal. There was no pulse elevation and no thyroid enlargement. Basal metabolism was not tested. Capillary examination showed a picture in all respects similar to Case 1, pictured in Fig. 3.

CASE 7.—M. O., a woman, aged 25 years, who had never been in good health, complained of "poor circulation" since childhood, manifested by cold hands and feet. She had always been nervous, and worried so much she thought it kept her thin. Since the age of 20 years she had had frequent colds, leaving her with a dry, unproductive cough most of the time. Moreover, she had almost constantly a feeling of soreness under the sternum.

Physical examination showed an alert, slender, prematurely gray woman; right kidney was palpable and tonsils were diseased. Otherwise physical

examination was negative. Blood count, urinalysis, blood Wassermann, chest Roentgen ray, sputum examinations, electrocardiogram and basal metabolism revealed nothing significant. The orthodiagram showed a heart 18 per cent below average size. A diagnosis of neurocirculatory asthenia and visceroptosis was made, and a pharyngitis suggested as cause of cough.

Capillary examination showed essentially the same picture as seen in Fig. 3.

CASE 8.—S. H., a woman, aged 28 years, had led a sheltered life and was apparently well until July, 1929, when she noticed increasing nervousness, tremor of the hands and nervous instability. She had lost some weight, and her hands and feet perspired a great deal, and at times felt numb and tingling, but never cold. The onset of symptoms followed by one year the birth of her only child. There was, however, no previous history of nervous strain.

Blood pressure was 110 systolic and 72 diastolic. Hemoglobin was 93 per cent and the red blood cell count 4,600,000. She had a slight tremor of the fingers, slightly enlarged thyroid and a tachycardia of 140 on admission. Examination was otherwise essentially negative. Examination of urine, blood sugar, blood urea nitrogen, basal metabolic rate, van den Bergh, electrocardiogram, blood Wassermann, chest Roentgen ray, fractional gastric analysis, all revealed nothing abnormal. While in the ward she wept over trivial circumstances, and her pulse fluctuated widely between 140 and 70. Her nervousness practically disappeared while in the ward. A diagnosis of neurocirculatory asthenia and simple goiter was made. Capillary examination showed a picture quite similar to Case 3.

Discussion. A functional "neurasthenic" quality appears to be the clinical common denominator found in these 8 patients. This has been present, except in Case 8, from early childhood. Peripheral vasomotor instability is a prominent symptom. It is true that one patient has an early arthritis, and another an essential hypertension, but many other patients examined with these conditions failed to show any morphologically abnormal capillary change. On the other hand, most of the patients diagnosed under one of the neurasthenia categories showed perfectly normal capillaries. In the present series, some 23 such patients were examined and found to be perfectly normal as concerns nail-bed microscopy. According to Muller, onset at an early age and the prominence of symptoms due to vasomotor instability are the two factors most suggestive of the syndrome he describes. The record of these 8 patients would somewhat support this. In the history of the other 23, with 2 exceptions, symptoms dated from an emotional or psychic shock and not from early childhood. Moreover, in this larger group, vasomotor symptoms were much less prominent. This difference could not have been due to leading questions, for in every case the same questions were asked and the history was elicited before capillary examination, and never amplified later.

Summary. 1. In the absence of any of the recognized peripheral vascular diseases, abnormal cutaneous capillary configurations as seen at the nail bed, are most apt to occur in conjunction with neurasthenic states.

2. In the present series of 31 cases of "neurasthenia" studied, 8 showed abnormal cutaneous capillary configurations. Of these 8, all but 1 dated their symptoms from early life. Of the remaining 23, only 2 had a similar early onset, the remaining 21 apparently being initiated later by a psychic or emotional shock.

3. Vasomotor symptoms were universally present to a marked extent in the 8 with abnormal capillaries, and either absent or present to a lesser extent in the remaining 23.

4. It would seem that abnormal configuration of nail-bed capillaries in the absence of any of the recognized peripheral vascular diseases, suggests a neurasthenic state dating from early life and a constitutional nervous instability.

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RAYNAUD'S DISEASE: A CRITICAL REVIEW OF MINIMAL REQUISITES FOR DIAGNOSIS.*

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The concept of the disease or disturbance first fully described by Raynaud has varied from that held by those who deny the existence of such an entity, to that held by those who include under the term

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all vascular disturbances associated with intermittent changes in color of the skin, and all grades of gangrene. The increasing amount of literature attests to the tendency to utilize the terms "Raynaud's disease" or "Raynaud's syndrome" as a general depository for a heterogeneous group of cases far removed from the condition originally described by Raynaud. Frequently in the literature one sees the statement "a typical case of Raynaud's disease," yet close examination of the report shows no similarity of the case presented to one of Raynaud's disease. The problem then resolves itself into this: should the diagnosis be reserved for a carefully defined condition, with characteristics sufficiently common to all cases for the condition to be designated as a disease, or should its boundaries be so extended as to include the larger and more inclusive group of vasospastic disturbances?

This study, then, attempts to review and analyze the cases reported by Raynaud to ascertain his allegiance to his criteria, to review a group of cases from the literature for the same purpose, and then to attempt to decide whether Raynaud's concept of this condition should be left unchanged or should be subject to certain revisions.*

Criteria of Raynaud. *The Occurrence of Gangrene Without Arterial Occlusion.* "I propose to demonstrate . . . gangrene affecting the extremities which it is impossible to explain by arterial occlusion" (page 8).† "There are gangrenes without alteration of vessels" (page 9). ". . . The variety of gangrene which I shall discuss . . . the arteries remaining permeable" (page 17). "All (of these gangrenes) present as a common character, absence of material obstruction to the course of the blood" (page 31). "The pulse never ceases to be perceptible . . . but it may present remarkable alterations" (page 107). "There actually occur . . . spontaneous vascular spasms, inappreciable in the great vessels, but very obvious in the arteries of small caliber" (page 155). "In symmetrical gangrene the pulsations (of the peripheral arteries) sometimes irregular, are ordinarily normal" (page 113).

Symmetry of Gangrene. "A variety (of gangrene) characterized especially by a remarkable tendency to symmetry . . . always affects symmetrical parts, the two upper or lower limbs, or the four at the same time; further in certain cases the nose and ears" (page 8). "I have been struck with the remarkable tendency of the mortification to affect symmetrically similar extremities . . . symmetrical parts which become affected together in a very great majority of cases. . . . Some (cases) deviate from the type more or less . . . but the tendency to localize itself at the same time

* If similar critical analyses were carried out in various eponymic diseases, such confusion would be avoided, in our opinion. [EDITOR'S NOTE.]

† The pages apply to the edition of Raynaud's work to which reference is made in the bibliography.

to the right and left halves of the body . . . would suffice, I think, to justify the titles of symmetrical gangrene" (page 98).

The Occurrence of Local Syncope. "One or more fingers become pale and cold all at once; in many cases it is the same finger which is always first attacked; the others become dead successively and in the same order. The attack is indolent; the duration varies from a few minutes to many hours. The cutaneous sensibility becomes blunted, then annihilated; the fingers become like foreign bodies to the subjects . . . , their temperature is notably lowered" (page 99).

The Occurrence of Local Asphyxia. "In the more pronounced cases, those in which the asphyxial symptoms predominate, the pallor of the extremities is replaced by a cyanotic color . . . sometimes it is bluish white, sometimes it is violet or slate colored, even becoming black" (page 101).

The Occurrence of Localized Rubor. "Finally (following cyanosis) a patch of red is formed on the extremities of the fingers. This patch gives place to normal pink color, and then the skin is found to have entirely returned to the primitive conditions" (page 101).

Type and Occurrence of Gangrene. "Sometimes the digits become entirely black and insensible, small phlyctenulæ appear upon one digit, . . . then on another, always at the extremity . . . . The small excoriation which results from it (the phlyctenula) persists some days. To see this lividity, this glacial cold, one would believe that the gangrene was about to extend more and more; but the malady recedes, the parts become reanimated, the small ulcer cicatrizes and contracts and there results a kind of conical tubercle immediately subadjacent to the nail" (page 105). "In a general way one may say that the most profound gangrenes are those which go to the length of causing the fall of many ends of fingers or toes" (page 108). "Symmetrical gangrene is mostly limited to the skin or to a very small extent beyond as, *e. g.*, to the extremity of the ungual phalanx" (page 113).

"Finally . . . we see gangrenous points appear on the extremities . . . may occupy the superficial layers of the skin from the extent of a pin's head up to the end of a finger, rarely more" (page 153). "The termination even in this grave form . . . is for the most part favorable. The sloughs detach themselves . . . cicatrization takes place" (page 108).

Intermittency of Attacks of Color Changes. "But it is . . . important . . . that cyanosis . . . related . . . to an organic lesion . . . the cause being permanent, the effect is also . . . there are no intermissions, although this obtains in local asphyxia" (page 102). "The attack (of pallor) is indolent, the duration varies from a few minutes to many hours" (page 99). "The period of reaction (from cyanosis) is accompanied by tingling sensations. . . . Livid patches appear on the cyanosed

parts. . . . This patch gives place to normal pink color" (page 101).

Review of Raynaud's Cases. There is no equivocation in Raynaud's statements as to the absence of organic arterial occlusion in the disease described by him. This absence of organic arterial disease is the chief premise presented by him. His entire thesis hinged on it. He believed, however, that diminished pulsation in the peripheral arteries, when present, was evidence of spasm. This doubtless allowed him to include cases of organic occlusive arterial disease in his two theses, for it has been shown[1,2,3] that organic disease of the digital arteries associated with vasomotor changes, may occur in the presence of normal or diminished pulsations in the usual palpable arteries; namely, radial, ulnar, dorsalis pedis, and posterior tibial.

It is interesting that in the presentation of 31 cases, in Raynaud's two theses, the state of pulsations in the peripheral arteries was not mentioned in 14 (45 per cent). If we hold to his chief premise of gangrene without arterial occlusion we must exclude Cases 1, 2, 4, 5, 7, 16, 17, 20, 21, 23, 24 and 25 in the first thesis, and Cases 4 and 5 in the second thesis, as presenting inadequate data regarding patency of arteries. Several of these cases are probably bona fide instances of Raynaud's disease. In an additional 4 cases (Cases 3 and 12 of the first thesis, and 2 and 6 of the second thesis) pulsations were diminished or absent in the peripheral arteries. Doubtless more cases could be added to this group if we included those in which palpation of the peripheral arteries, for pulsation, was inadequate. In several instances, Raynaud wrote, "pulsations were perceptible," but he did not designate which arteries were palpated or whether pulsation was diminished. We know that gangrene due to arteriosclerosis or thrombo-angiitis obliterans may occur in the presence of normal or slightly diminished pulsations in some of the peripheral arteries. The incomplete observations, and the failure to recognize diminution in pulsation as evidence of organic disease of the arteries, doubtless led to his statement: "The absence of arterial occlusion has only a negative value and also applies to diabetic gangrene" (page 98).

Case 3 in Raynaud's first series deserves special consideration. A young soldier had had dropsy at the age of 16 years and had been short of breath thereafter. On the night of admission to the hospital numbness of the left arm developed, the radial pulse was barely palpable, and the extremity was white and cold. Five days later, a similar condition developed in the right arm. Raynaud's assumption that the cause of the disturbance was a functional lesion which extended from the capillaries to the arteries, that is, to a spasmodic state of the arteries, appears unwarranted. The history of edema, dyspnea, and sudden onset of distress in first one and then the other arm, with diminished or absent pulsation in the

radial arteries, almost certainly represents arterial embolism, probably of cardiac origin.

It is perhaps understandable how such a brilliant investigator, presenting evidence of gangrene without organic occlusion of the arteries, could fail to record the status of the peripheral vessels, for some of the records were collected from the literature and the patients were never seen by Raynaud (page 31). Only 5 of the 25 cases presented in 1862 were Raynaud's own cases, but careful scrutiny of the records of these 25 cases indicates that he probably observed an additional 5, a total of 10, or less than 40 per cent of all cases the records of which are given. In 3 of these 10 cases, however, the state of pulsation in the peripheral arteries is not given. In the second thesis Raynaud presented 6 cases, all of which he observed personally; there were 2 in which absent or diminished pulsations were noted and 2 in which the state of pulsations was not given.

If one examines closely the significance of the term gangrene as used by Raynaud, one finds an entirely different connotation than that of many later authors. Raynaud described loss of tissue localized to the ends of the digits and wrote: "Symmetrical gangrene is mostly limited to the skin . . . small phlyctenulæ always on the ends of the digits . . . the most profound gangrenes (are) those which go to the length of causing the fall of many ends of fingers or toes." He differentiated clearly (page 113) senile gangrene (which is due to an occlusive arterial lesion the same as it is in thrombo-angiitis obliterans) and symmetrical gangrene of Raynaud's disease; yet many cases of so-called Raynaud's disease in contemporary literature are obviously examples of occlusive arterial lesions. The reason for this confusion must in part be laid at Raynaud's door because the gangrene described in several of his cases varied greatly from that described in his original definition. In his first thesis, in Case 13 there were lesions on the heels, and in Case 14 the ends of some fingers, to the first joint, had been lost. In Case 16, there was complete gangrene of the ends of the fingers and toes, to the second phalanges, and amputation was necessary. In Case 17 dry gangrene of all fingers and toes was present; in Case 18, gangrene of both feet; in Case 19, ulcers on the legs and sloughs on the dorsum of the feet; in Case 21, all toes and many fingers had been lost with gangrene; in Case 22, dry gangrene extended as high as the elbows and as high as the ankles, and there was gangrene of cheeks and miliary eruptions over the body; in Case 23, there was gangrene of the entire left hand, shoulders, thigh, etc; in Case 24, gangrene of many fingers and of both feet had resulted in spontaneous amputation; in Case 25, both arms were gangrenous to the elbows. In the second thesis, in Case 6, the patient had suffered spontaneous loss of the toes from gangrene. Here, then, are 12 cases, in each of which the gangrene far exceeded

in degree and extent that described by Raynaud as the maximal gangrene which might occur in the disease he was describing. In these 12 reports, the state of the pulsations in the peripheral arteries was recorded in only 2; namely, in Case 18 (first thesis) in which freezing as an etiologic factor could not be excluded, and in Case 6 (second thesis) in which there was definite arterial occlusion. This group is comprised of two-thirds of the total 18 cases in which pulsations in the peripheral arteries were diminished, absent, or not mentioned. They can all be excluded from any consideration of Raynaud's disease because in 7 cases the gangrene exceeded in extent and severity that which Raynaud described as being characteristic of the disorder on which he was writing and because the state of pulsations in the arteries was diminished, absent or not mentioned.

Case 11 (first thesis) was probably an example of scleroderma with vasomotor changes, but otherwise it meets the requirements laid down by Raynaud.

Raynaud is hardly consistent as regards symmetry of gangrene, for he wrote that the gangrene displays "remarkable tendency to symmetry;" that it "always affects symmetrical parts;" that it involves "symmetrical parts which become affected together in the great majority of cases" and that "some (cases) deviate from the type (symmetry) more or less." This uncertainty is well illustrated, for Cases 4, 10, and 3 of the first thesis, and Case 6 of the second thesis present asymmetry. That all of these cases were authentic examples should be questioned. In Case 4 there was only recurrent syncope, and the condition of pulsations in the arteries was not given; cervical rib was not excluded. In Case 10 there was only a dry slough on the extremity of one toe, with no preceding changes in color. Case 3 had been discussed already as an example of arterial embolus of cardiac origin, and in Case 6 of the second thesis there was extensive gangrene and arterial occlusion. There seems adequate basis, other than asymmetry, in each case, to exclude it from consideration as an example of the type of disease Raynaud described in the text of his two theses.

There remains, however, a practical certainty that the condition which should be known as Raynaud's disease is always bilateral, and this conforms to our observations of more than 150 cases. Moreover, this bilaterality must indicate simultaneous involvement of symmetrical parts, for Raynaud described the phenomenon of "(symmetrical parts) affected together" and "the tendency (of the gangrene) to localize itself at the same time to the right and left halves of the body." Emphasis must be laid here on the words "together" and "at the same time." Obviously it was not Raynaud's intent that the term symmetrical gangrene should apply to gangrene occurring in one extremity weeks or months before involvement of its homologous member of the opposite side. This

should be borne in mind when speaking of symmetrical gangrene. He intended the word "symmetry" to connote simultaneous symmetrical involvement. It is apparent that close adherence to this tenet of simultaneous symmetry alone would obviate a large share of the confusion which surrounds the diagnosis of Raynaud's disease.

In 16 of the cases (53 per cent) presented by Raynaud in both theses taken together, intermittent changes in color were not exhibited. All of these could be eliminated on other grounds: asymmetry, too extensive gangrene or a failure to note the presence or absence of pulsations in the peripheral arteries.

TABLE 1.—CASES REPORTED BY RAYNAUD WHICH DID NOT CORRESPOND WITH THE SYNDROME DESCRIBED BY HIM.*

	Features not characteristic of Raynaud's syndrome.			
Case.	Asymmetrical abnormalities present.	Gangrene of excessive degree or extension present.	Arterial pulsations absent, definitely diminished, or not reported.	Intermittent color changes absent.
First thesis:				
1	..	..	Yes	
2	..	..	Yes	
3	Yes	..	Yes	Yes
4	Yes	..	Yes	
5	..	..	Yes	
7	..	..	Yes	Yes
10	Yes	..	..	Yes
11	..	(scleroderma)		
12	..	..	Yes	Yes
13	..	Yes	..	Yes
14	..	Yes	..	Yes
16	..	Yes	Yes	Yes
17	..	Yes	Yes	Yes
18	..	Yes	..	Yes
19	..	Yes	..	Yes
20	..	..	Yes	Yes
21	..	Yes	Yes	Yes
22	..	Yes	..	Yes
23	..	Yes	Yes	Yes
24	..	Yes	Yes	Yes
25	..	Yes	Yes	Yes
Second thesis:				
2	..	..	Yes	
4	..	..	Yes	
5	..	..	Yes	
6	..	Yes	Yes	Yes

* Cases 6, 8 and 9 of Raynaud's first thesis and Cases 1 and 3 of his second thesis corresponded with the syndrome described by him. Case 15 of the first thesis may have corresponded with the syndrome, but whether or not it fulfilled the condition of displaying intermittent color changes is questionable.

Critical examination of Raynaud's cases, then, on the basis of essentials laid down in the text of his theses, requires us to exclude (Table 1) all but 6 (Cases 6, 8, 9 and 15 of the first thesis, and Cases 1 and 3 of the second thesis). In addition, Cases 1 and 2 of his first thesis and Cases 2, 4 and 5 of his second thesis fill all the require-

ments for the diagnosis of Raynaud's disease except that the state of pulsation in the peripheral arteries is not noted. Some of them, particularly Cases 1 and 2 of the first thesis, are probably instances of a mild type of the affection. In Case 2 of the second thesis the radial artery was diminished in caliber during an attack of change in color. This may occur when Raynaud's disease or when organic arterial disease is present.

When the acceptable cases are examined to determine their common symptoms, it is seen that all 6 were personally observed by Raynaud. Paroxysmal attacks of pallor, or cyanosis, or both, were noted in all instances. This is important, for intermittency of changes in color was not used by us as a basis for accepting these cases as true instances of the disease which Raynaud was describing. Of the 25 cases excluded as not being typical of Raynaud's disease, excluded, that is, on the basis of considerations other than intermittency of changes in color, in 16 (64 per cent) intermittent changes in color were not noted. In Case 1 of the second thesis, visual disturbances, with narrowing of the retinal arteries, were observed during or shortly after evidence of the attack as seen in the extremities. Involvement of the nose or ears by cyanosis was observed in three instances (Cases 8, 6 and 15, first thesis). Exposure to lower temperature as the immediate cause of the attacks of cyanosis or pallor was noted in Cases 1 (second thesis) and 6 (first thesis).

In the 6 acceptable cases, 5 patients were women, aged 22, 27, 28, 30 and 52 years, respectively; the man was aged 59 years.

Now, after a critical survey of Raynaud's cases and the material in the text of his two theses, we may proceed to the definition of the disease named after Raynaud. His own special criteria are as follows: "In slight cases the fingers and toes become cold, cyanosed and livid and at the same time more or less painful. In grave cases the area affected by cyanosis extends upward for several centimeters above the roots of the nails; at the same time the nose and ears may become the seat of analogous phenomena. Finally, if the state is prolonged for a certain time, we see gangrenous points appear on the extremities; the gangrene is always dry and may occupy the superficial layers of the skin from the extent of a pin's head up to the end of a finger, rarely more. That which gives to this malady its special feature is the remarkable symmetry which the lesions manifest. . . . This interesting peculiarity taken with intermittency of attacks in many cases would in itself justify the belief that there exists no material obstacle to the course of the blood in the arteries." Here is the meat of Raynaud's entire presentation, a definition which, as has been shown, excludes many of his cases. Close adherence to the fundamentals laid down in this definition would eliminate the confusion which has existed, and the definition demonstrates clearly that most cases in the literature are not of a type that would meet the description given by Raynaud. Unfortunately, cases

reported by Raynaud have too often served as models for later authors without due consideration of the fact that many of Raynaud's cases did not meet the fundamental tenets of his researches. Too much weight has been given to the words "gangrene symmetrique" in the title of Raynaud's first thesis, in spite of the fact that the full title reads "L'asphyxie local et de la gangrene symmetrique." Raynaud later attempted a correction of this error, for he wrote in his thesis of 1874: "May I now be allowed to criticize the name which I gave the disease . . . local asphyxia and symmetrical gangrene are not two distinct maladies but two degrees of the same malady . . . the second is often absent."

The loose application of the term "Raynaud's disease" has been emphasized by Cassirer, who wrote:* "Those who have reported cases of this kind since Raynaud, have not by any means limited themselves to inclusion of the important characteristics of the affection, which were given by Raynaud. Cases have been described particularly by English authors, which had hardly a single characteristic in common with those originally given by Raynaud; symmetry and preceding vasomotor appearances were absent; the vascular system was not intact; the gangrene occurred in the course of an infectious disease and spread widely and much more."

Raynaud's disease in men and children is rare in our experience; yet it is commonly reported. In order to demonstrate the type of case which has crept into the literature under the title of Raynaud's disease, we present a study of 25 unselected cases in men or children from the German, English, and American literature (Table 2). In these 25 cases, the condition of the pulsation in the peripheral arteries was not noted in 18, was normal in 1, and absent or markedly diminished pulsations were noted in 7 cases. Consideration of these 25 cases from the standpoint of simultaneous, symmetric involvement, with discoloration or gangrene, reveals the following: symmetry was present in 13 cases, absent in 11 cases and not noted in 1 case. Gangrene was present in 15 of the 25 cases but exceeded the maximum described by Raynaud in 10 cases. Frequently the gangrene had been so extensive that amputation of a leg at the midfemoral region had been necessary. Cyanosis or pallor was described in 15 of the cases, of which 9 had constant changes in color and 6 intermittent changes in color. Posture influenced the color markedly in 2 cases in which changes in color were intermittent. In 1 case, change in color appeared only when the patient was using a pneu-

* "Diejenigen die nach Raynaud über derartige Krankheitsfälle berichtet haben, haben sich in ihren Diagnosen keineswegs immer an diese von Raynaud gegebene Feststellung der wichtigsten Züge der Affektion gehalten; und es sind, namentlich von englischen Autoren unter dem Namen Raynaudsche Krankheit Fälle beschrieben worden, die kaum noch einen Zug mit dem ursprünglichen Krankheits-bilde der Raynaudschen Affektion gemeinsam hatten: da fehlte die Symmetrie und die vorausgehenden vasomotorischen Erscheinungen; das Gefässsytem war nicht intakt, die Gangrän trat im Laufe einer Infektionskrankheit auf, dehnte sich weit aus, und anderes mehr."

TABLE 2.—SUMMARY OF TWENTY-FIVE UNSELECTED CASES FROM GERMAN, ENGLISH AND AMERICAN LITERATURE WHICH WERE PRESENTED AS EXAMPLES OF RAYNAUD'S DISEASE IN MEN OR CHILDREN.

Age (years) and sex.	Clinical history.	State of pulsations in peripheral arteries.	Probable diagnosis.*
32 (M)	Right hand cyanotic; left hand blue and cold, with impending gangrene	Absent in left radial, markedly diminished in right radial	Thrombo-angiitis obliterans
(M)	Two months of swelling and stiffness of hands; hands to above wrists stony and wooden with fixation of joints; crater-like ulcers on finger tips	Not mentioned	Scleroderma
32 (M)	Two years of severe pain in leg and foot; varicose veins and superficial phlebitis; gangrene of great toe, with edema of lower third of leg	Not mentioned	Thrombo-angiitis obliterans
60 (M)	Amputation of both legs for gangrene; uncontrolled diabetes	Absent in dorsalis pedis and posterior tibial bilaterally	Arteriosclerotic or diabetic gangrene
Child (F)	Chorea with involvement of heart; auricular fibrillation; sudden pain in left foot with pallor and coldness; similar events in right foot the following day; gangrene of right foot with amputation	Not mentioned	Embolism of cardiac origin
43 (M)	Local asphyxia of fingers of left hand with gangrene of last phalanx of index finger and tip of third finger	Not mentioned	Thrombo-angiitis obliterans
45 (M)	Weakness and tingling of right hand; pallor of hand with elevation or immersion in cold water; cyanosis when dependent	Absent in right radial and ulnar diminished in right brachial and subclavian	Thrombo-angiitis obliterans with vasomotor changes
48 (M)	Between 1906 and 1914 amputation of right first and fifth toes, right foot, right leg, left first, second and third toes, right first, second and third fingers for gangrene and pain	Not mentioned	Thrombo-angiitis obliterans
26 (M)	Pallor and coldness of index and middle fingers when using pneumatic stone cutter which vibrated 900 to 1600 times each minute	Not mentioned	Vasomotor changes effected by rapid vibration
40 (M)	Pains in fingers and toes, with swelling and lividity; fingers and toes numb; tips of fingers and toes black	Not mentioned	Thrombo-angiitis obliterans
37 (M)	Amputation of left first and fifth toes for gangrene and pain; ulcer on left third toe; fingers and toes blue at times	Not mentioned	Thrombo-angiitis obliterans
38 (M)	Attacks of pallor and cyanosis of fingers; amputation of left first and second toes for gangrene and pain; no healing	Slight, bilaterally in dorsalis pedis	Thrombo-angiitis obliterans with vasomotor changes
51 (M)	"Typical" fingers and toes with high-grade ischemia and anesthesia of digits	Not mentioned	Insufficient data

Child 9 days	Cyanotic at birth; blisters on mouth, gangrene of all extremities; necropsy disclosed intra-auricular septal defect, and stenosis of isthmus of aorta; arteries and veins of extremities appeared normal	Pulsations not mentioned; arteries normal at necropsy	Congenital heart disease and unknown factors
34 (M)	Pain in right foot and leg for three years while walking; pain in left fifth toe; removal of toenail with no healing; superficial phlebitis; death after Leriche operation; necropsy not done	Not mentioned	Thrombo-angiitis obliterans
(M)	Froze both feet 5 years before report was made; for 3 years previous to report feet had tired easily; amputation of right leg for pain in the right foot; pain in the right hand and cracking of skin on finger tips, with gangrene	None in either radial	Thrombo-angiitis obliterans
33 (M)	Six years previous to report right great and left second toes sloughed after severe pain and gangrene; 1 year previous to report, right and left middle fingers painful, swollen and gangrenous; right middle finger amputated	In dorsalis pedis and radial bilaterally, varied from absent to normal; pathologic changes in arteries of amputated finger	Thrombo-angiitis obliterans
36 (M)	Blueness of ears, fingers, hands and legs to the knees; multiple areas of cutaneous gangrene over shoulders, arms, forearms, hands, fingers, hips, knees, legs, toes and scrotum	Not mentioned	Indeterminate
40 (M)	Dermatitis herpetiformis for 1 year; then brown, anesthetic spots on two distal phalanges of right middle finger; 6 weeks later, recurrent attacks of cyanosis and pallor of all finger tips on left hand; later dry gangrene in these regions	Not mentioned	Indeterminate
60 (M)	Pain and blueness of fingers; cracks around finger nails; rheumatic pains in arms and mottling of skin of both forearms; at necropsy, carcinoma of stomach with metastasis to inferior cervical ganglion found	Normal in dorsalis in pedis and radial, bilaterally	Indeterminate
35 (M)	Amputation of right first and second toes, and 2 fingers for pain and gangrene, very slow healing; amputation of left first and right third toes, no healing	Not mentioned	Thrombo-angiitis obliterans
39 (M)	Cyanosis, pain and coldness in extremities for 3 years; color relieved by elevation, increased by dependency; ulcer on left great toe for 6 months	Not mentioned	Thrombo-angiitis obliterans
39 (M)	Four months of purple discoloration of hands with gangrene of left first and third fingers; severe pain	Not mentioned	Thrombo-angiitis obliterans
41 (M)	Rust-red discoloration of fingers followed by swelling and pain; both great toes swollen and tender with gangrenous areas on each; severe pain	Not mentioned	Thrombo-angiitis obliterans
33 (M)	Angina pectoris and intermittent claudication	Not mentioned	Thrombo-angiitis obliterans with involvement of coronary arteries

* Made by Allen and Brown.

matic tool, in another it appeared usually in the morning, in 1 case it was noted with exposure to cold, and it appeared spontaneously in 1 case.

Many cases were obviously instances of peripheral occlusive arterial disease, and in the history intermittent claudication had been noted or suggested, as well as superficial phlebitis and absence of pulsation in the peripheral arteries.

Our tentative diagnoses, made from the histories and observations given in the reports, are distributed as follows: thrombo-angiitis obliterans, 16 cases; unknown, 4; arteriosclerosis, 1; embolism, 1; vasomotor changes associated with rapid vibration of extremity while using a pneumatic tool, 1; congenital heart disease, 1; multiple cutaneous gangrene (not limited to extremities) with cyanosis of extremities, 1, and Raynaud's disease, none.

It is admitted that diagnoses made from reports of cases, without the privilege of examining the patient, are subject to a high error, but the finding that none of these 25 cases fulfills the requirements laid down in Raynaud's theses is pertinent. It is admitted that some of the cases simulate some of those described by Raynaud, but, as previously pointed out, many of Raynaud's cases did not meet his own minimal requirements. In fact, he characterized many of them as questionable or undefined types of cases.

Comment. Since Raynaud made his classical description of the disease which bears his name, further clarification has been made in the group of peripheral vascular diseases. Thrombo-angiitis obliterans has been identified and accepted as an entity, and embolic occlusion of the peripheral arteries, gangrene and trophic changes due to medicaments are better recognized. Of significance is the recognition that vasomotor symptoms are more often secondary phenomena than primary. These symptoms frequently accompany organic disease of the arteries; hence, vasomotor disturbances only do not constitute a diagnosis of Raynaud's disease. It is admitted that our knowledge is still defective, and cases occasionally do not permit of accurate differentiation or classification. Such a case should be presented as an unusual or atypical case and not given the name of a condition to which it obviously does not belong. Some of these cases may represent new or previously undescribed syndromes.

It is obvious that confusion and not advancement of knowledge is served by departing from the criteria stated by Raynaud. If this disease is to remain an entity, it must have some boundaries. Other explanations must be found for the cases which depart from the prescribed limits.

From our group of 150 carefully studied cases, in all of which complete neurologic examination was done and careful notation of the patency of the peripheral arteries was made and reëxamined

after long intervals, we are convinced that there is a definite primary disease or disturbance which can be called Raynaud's disease. The minimal requirements for diagnosis are those originally stated by Raynaud: (1) intermittent attacks of discoloration of extremities: (2) absence of evidence of organic arterial occlusion; (3) symmetric or bilateral distribution, and (4) trophic changes, when present, limited to the skin and never consisting of gross gangrene.

Secondary criteria are as follows: (1) predilection for females, such that more than 90 per cent of cases appear in persons of this sex, and (2) absence of pain is so striking that severe pain during the attacks is exceptional, and its presence militates against the diagnosis of a primary vasomotor disturbance of the spastic type.*

In addition to these diagnostic requisites, exclusion of any primary disease that in itself can give rise to vasospastic symptoms is of primary importance. Arthritis, neuritis, cervical rib, thromboangiitis obliterans, arteriosclerotic disease, and other diseases, are at times associated with disturbances of color of the hands or feet. The large incidence of this disease in females makes its diagnosis in the male at best tentative. In our experience, in cases in which diagnosis of Raynaud's disease in the male has been made early, and in which these patients have subsequently been traced, evidence of organic occlusion of the peripheral arteries usually has been found. Likewise in cases of gangrene of greater extent than epidermal gangrene; that is, gangrene involving a digit, pathologic examination has disclosed thrombosis of the type which we recognize as thrombo-angiitis obliterans. In fact, gangrene in Raynaud's disease is relatively rare; probably in 20 per cent of cases the patients suffer definite loss of tissue, and this frequently consists of minute excavations without symptoms. The more severe grades of gangrene take the form of felons or suppuration of the digits, and frequently are associated with sclerodermal changes in the skin of the digits.

If the field of peripheral vascular diseases is to assume its rightful place among other branches of medicine, the same care must be manifested as that which brought order out of chaos in other fields and elevated them to their present high level. Adequate care in diagnosis is important not only from an academic standpoint, but from a practical standpoint as well. Inadequate examination is responsible for many errors in diagnosis. To diagnose Raynaud's disease without determining the state of pulsation in the peripheral vessels is comparable to diagnosing mitral stenosis without listening to the heart. Unless due caution is exercised, operative measures

* Lewis has, on the basis of careful experiments, postulated that Raynaud's disease does not have a vasomotor basis, but that a local fault of the digital arteries is the underlying disturbance. Simpson, Brown and Adson's work shows that in the early uncomplicated case, a vasomotor basis exists, but in the later or complicated case a local disturbance of the arteries is also present.

on the sympathetic nerves, which induce a high percentage of cures in properly diagnosed cases, may be subjected to undue criticism and fall into disrepute.

Conclusions. Raynaud described a clinical syndrome which justifiably bears his name. His requirements for diagnosis are valid and are borne out by our studies of more than 150 cases. These requirements are: (1) Gangrene or trophic changes limited in a large degree to the skin; (2) symmetrical or bilateral involvement; (3) absence of evidence of occlusive lesions of the peripheral arteries, and (4) intermittent attacks of changes in color which usually precede the trophic changes by months or years.

Many of the cases reported by Raynaud were not illustrative of the condition described by him, as is usually the case with eponymic diseases described many years ago. They did not fulfill the minimal requirements. The use of these cases as models by many subsequent authors has led to a high percentage of erroneous diagnoses.

Study of 25 cases reported in the literature as Raynaud's disease shows that none of them fulfills the necessary requirements for such a diagnosis. These cases are characterized by failure to adhere to Raynaud's basic requirements, and inadequacy of examination of patients. Many of the cases are obviously examples of thrombo-angiitis obliterans.

Accurate diagnosis in peripheral vascular disease is essential if treatment is to be properly evaluated.

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ERYTHREMIA AND MYELOGENOUS LEUKEMIA.

REPORT OF CASES PRESENTING ASPECTS OF BOTH DISEASES.

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WHILE there is generally little difficulty associated with the diagnosis of erythremia, there are cases reported in the literature which present a composite picture of both polycythemia and myelogenous leukemia. In these instances it is often exceedingly difficult to make a differential diagnosis. Indeed the answer is, more often than not, in doubt until after the postmortem examination.

Pendergrass and Pancoast,[1] Minot and Buchman,[2] Harrop[3] and A. Horstrup[4] have reviewed the literature and considered the significance of the composite picture of polycythemia and myelogenous leukemia.

The first case is reported because of the unusual blood picture, the course during treatment, and the postmortem findings. Besides 36 cases of myelogenous leukemia and 11 cases of erythremia appearing in the records of the Peter Bent Brigham Hospital, there are 4 others which combine features of both diseases. The records of these also are presented briefly.

Case Reports. CASE 1.—W. J. G. (P. B. B. H. Med. 36155), aged 50 years, white, single, Canadian-American, refrigerator engineer, entered the hospital December 20, 1929, complaining of pains in the knees, calves and feet of 4 months' duration. Twenty years before admission he suffered a depressed fracture of the skull, from which an uneventful recovery was made. Four months before entry the patient's knees became painful, red and swollen. Shortly after, an enlarged spleen was found. Three months before admission the right foot became painful, and numbness was noted in both feet for the first time. The numbness gradually extended upward to the knees. With it, he began to have shooting pains extending from the toes and feet into the calves of both legs. These were worse at night. Walking caused the soles of his feet and the lateral aspects of both knees to pain. Since the onset of the present illness he has lost 30 to 40 pounds, weighing 127 pounds on admission.

Physical examination revealed a well-developed, undernourished, white male. He was mentally clear. The face had a florid, erythremic appearance with a suggestion of right facial weakness. The lips, nail beds and tongue were slightly cyanotic. The skin was warm and florid. There was a small, irregular depression in the left parietal region of the skull. The fundi were not unusual; the vessels were not turgid, nor the retina more

colored than normal. The diaphragm was high on the left side, giving dullness at the base of the lung in front, back and axilla, approximately 2 interspaces higher than normal. Posteriorly there were medium, crepitant râles at the left base on deep inspiration. Stereoscopic Roentgen ray examination showed the lungs to be clear. The diaphragms were dome-shaped, with the left diaphragm limited fluoroscopically. Stereoscopic Roentgen ray examination of the lumbar spine and pelvis revealed no abnormality. The heart and peripheral vascular system were not remarkable. The blood pressure was 120 systolic and 90 diastolic. The entire left half of the abdomen was filled with a firm, nontender, smooth mass, presumably the spleen, which pushed up the diaphragm, extended down below the anterior superior spine of the pelvis and a short distance across the midline to the right. The liver did not appear enlarged. There was no lymphadenopathy. The reflexes were normal. Hyperesthesia of the soles of both feet was present. Using a G-48 tuning fork, vibratory sensibility

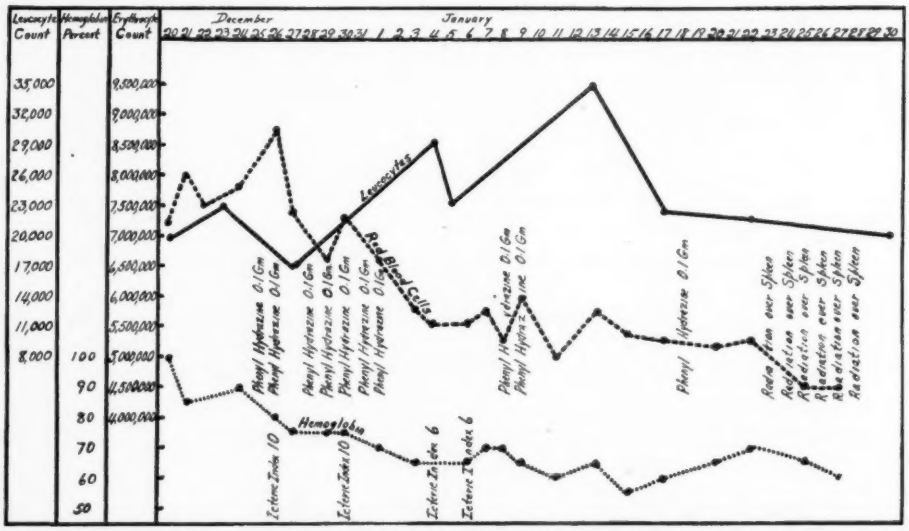

CHART I.—Case 1. Variations of blood elements in relation to treatment.

was lost in both legs but present in both iliac crests. Position sense, pain and touch seemed normal in both legs. There was no ataxia.

The *urine* occasionally showed a few hyalin and finely granular casts. The specific gravity ranged between 1.014 and 1.018. The phenolsulphonephthalein test gave an excretion of 60 per cent in 2 hours and 10 minutes in 300 cc. of urine. The *stool* examination was negative. *Gastric analysis*, using the Ewald test meal, revealed no free hydrochloric acid, and total acidity ranging between 15 and 22 units of 0.1-N sodium hydroxid in specimens of a fractional test. There was a positive benzidin reaction for occult blood in 4 of the 5 specimens.

Blood Studies. The Wassermann, Hinton and modified Hinton reactions were negative. Blood culture was negative. Clotting time by the 6-tube method was 15 minutes (normal control 6 minutes). The bleeding time was 2½ minutes by the method of Duke. Platelet count was 740,000 (Wright and Kinnicutt method). Fragility test: beginning hemolysis in 0.46 per cent NaCl; complete hemolysis in 0.28 per cent at the end of 2 hours. At the

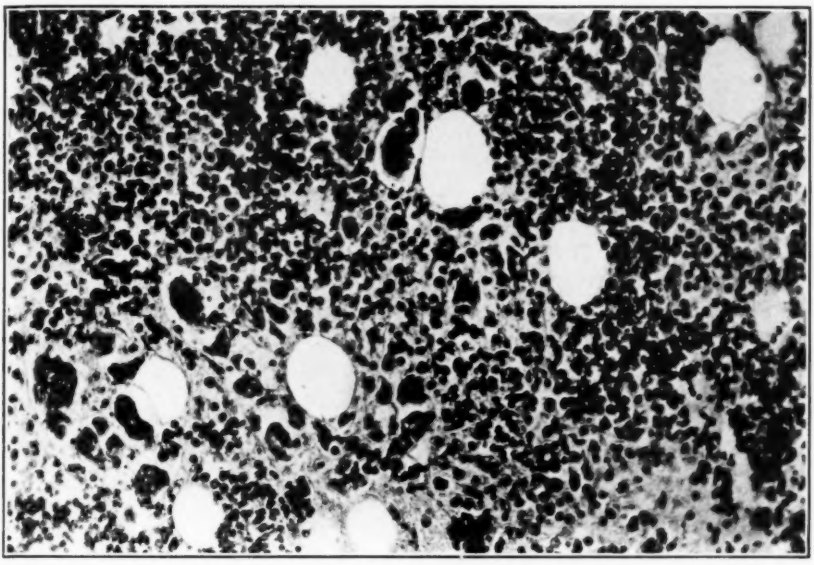

FIG. 1.—Case 1. Bone-marrow from femur. The section shows congestion of the marrow, scarcity of fat, hyperplasia of erythropoietic and leukocytic elements, and numerous megakaryocytes. × 300.

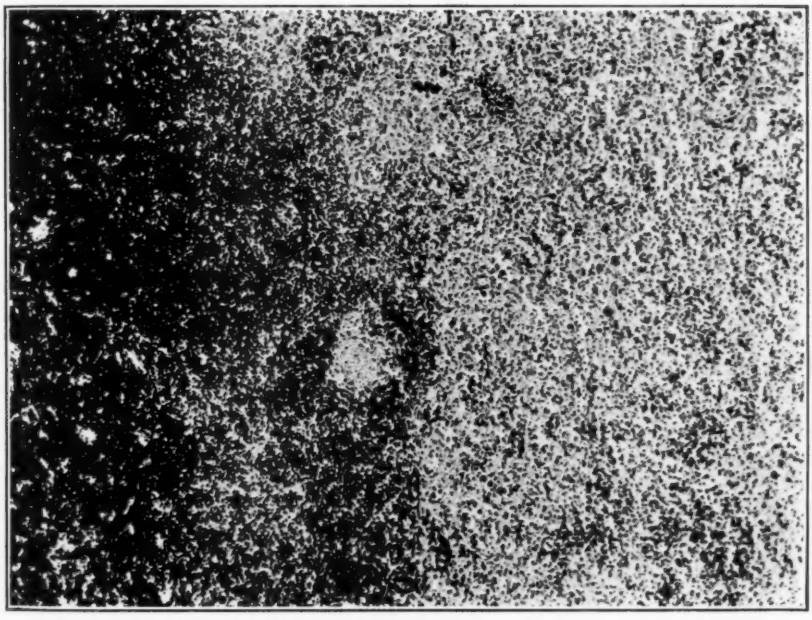

FIG. 2.—Case 1. Spleen. Congestion and diffuse fibrosis with prominence of trabeculæ and diminution of the lymph follicles is shown. The dark area at the left represents hemorrhage. × 110.

end of 10 hours: beginning hemolysis in 0.50 per cent; complete hemolysis in 0.28 per cent. Normal control: beginning hemolysis in 0.46 per cent; complete hemolysis in 0.30 per cent at the end of 2 hours. After 10 hours, beginning hemolysis in 0.46 per cent and complete hemolysis in 0.38 per cent. The variation in hemoglobin, red cells, white cells, and icteric index in relation to treatment with phenylhydrazine and Roentgen rays are depicted on the chart.

The hematocrit findings were as follows:

	R. B. C. count.	Cells, per cent.	Plasma, per cent.	Indiv. cell vol. 10–11 cu.cm.,
December 22 . . .	7,585,000	53.3	46.7	7.1
December 26 . . .	6,900,000	52.8	47.2	7.6
January 3	7,900,000	53.8	46.2	6.8

The differential blood counts and the results of the study of the blood smears are summarized in Table 1.

Clinical Course. On admission the patient's temperature was 98.8° F. and the pulse rate was 65. On the evening of December 23 the patient's temperature rose to 99.5° F. The next morning it was normal. He was given the first dose of 0.1 gm. phenylhydrazin. That evening the temperature began rising, reaching 102° F. on December 25. There was no jaundice nor rise in the icteric index. By December 27 the temperature had returned to 99° F. and the administration of phenylhydrazin was resumed without untoward effects. The excruciating pains in his knees and calves, complained of on admission, continued. On account of the fall in hemoglobin and red count the phenylhydrazin was discontinued for a week, beginning January 1. Beginning about January 17 it was noted that the pain in his legs was abating. During the course of treatment with phenylhydrazin it was noted that the florid, erythremic appearance was gradually disappearing, giving way to a progressive pallor. The spleen showed a definite decrease in size, although on January 23 it was still below the umbilicus. On January 23 a course of Roentgen ray therapy was commenced. This consisted of a maximum suberythema dose over the splenic area anteriorly and posteriorly. This is calculated as 750 "r" measured in air with a Duane ionization chamber, and is given in 6 divided doses of 250 "r" each on 6 successive days. On January 29, after having received the course of 6 Roentgen ray treatments, he suddenly became mildly disoriented. He complained of excruciating pains shooting down his legs and began having seizures of generalized trembling, spasmodic movements and stiffening of the entire body. These attacks continued for 24 hours. The suggestive right facial weakness found on admission became more pronounced. His pulse gradually became slower and weaker and on the evening of January 30 he died.

Postmortem Examination. The general appearance of the body was essentially normal. The heart weighed 360 gm. and was essentially normal. The lungs showed moderate congestion and edema, obsolete tuberculous lesions at both apices, but no evidence of bronchopneumonia or emphysema.

The spleen weighed 1220 gm. Its consistency was very soft. The capsule was thickened, smooth, moist and glistening, with numerous irregular, firm, yellow areas, representing old infarcts. The parenchyma was soft, pultaceous and of a uniform dull-red color with a tinge of pale gray, suggesting the color of ordinary red brick. No characteristic splenic markings were recognizable. On microscopic section (see photomicrograph) the spleen showed primarily fibrosis, congestion with scattered areas of hemorrhage and infiltration with abnormal types of cells. The Malpighian corpuscles were completely obliterated by the congestion and diffuse overgrowth of connective tissue. Rarely a cluster of lymphocytes was seen

TABLE 1.—CASE 1. BLOOD COUNTS AND BLOOD SMEARS IN A CASE OF ERYTHREMIA.

Date.	Red blood cells and hemoglobin.	White blood cells.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.	Abnormal white cells, per cent.	Red cells.
December 20, 1929	7,230,000 100%	19,800	49	8	0	5	0	Metamyelocytes, 28 (N, 19; E, 6; B, 3) Myelocytes, 10 (N, 7; E, 3)	Moderate achromia; moderate anisocytosis and poikilocytosis; platelets increased.
December 21, 1929	8,070,000 85%	23,000	53	9	1	8	6	Metamyelocytes, 9 Myelocytes, 3 Unclassified smudges, 11	As above; 2 nucleated red blood cells.
December 27, 1929	7,420,000 75%	16,800	65	10	2	4	4	Myelocytes, 4 Unclassified smudges, 11	As above; 1 nucleated red blood cell seen; reticulocytes 0.8 per cent.
January 4, 1930	5,520,000 65%	29,200	67	5	1	4	6	Metamyelocytes, 10 Myelocytes, 7	Moderate achromia; marked anisocytosis and poikilocytosis; no nucleated red blood cells; platelets increased.
January 13, 1930	5,730,000 65%	34,800	65	10	2	8	6	Myelocytes, 9	As above.
January 22, 1930	5,350,000 70%	21,500	64	1	1	1	7	Young polys, 10 Metamyelocytes, 8 Myelocytes, 7 Myeloblasts, 1	Marked achromia; marked anisocytosis; young microcytes and macrocytes; many tail forms.
January 27, 1930	4,440,000 60%	10,000	46	0	2	6	3	Young polys, 27 Metamyelocytes, 7 Myelocytes, 2 Unclassified smudges, 7	As above; no macrocytes.

near a central artery, representing the remains of an old splenic follicle. The trabeculæ were more prominent than usual due to the increase in connective tissue. The central arteries were sclerotic and not easily found. The infiltration of abnormal blood cells was the most significant feature of the microscopic picture. There were myeloblasts, neutrophilic and eosinophilic myelocytes, mature neutrophils, eosinophils and nucleated red blood cells. There were also many macrophages, endothelial leukocytes and a few large cells resembling megakaryocytes. The abnormal cells tended to occur in clusters or in small focal areas. Erythropoiesis was not a prominent feature.

The liver weighed 2255 gm. The gross appearance of the organ and capsule was normal. The cut surface showed a striking fine granularity. The parenchyma was softer and more friable than normal. There were no white spots indicative of leukemic infiltration. Sections of the liver showed marked congestion and infiltration of a few periportal spaces by lymphocytes, plasma cells and an occasional eosinophilic myelocyte. The dilated sinusoids and portal areas contained small numbers of leukocytes, resembling mostly neutrophils and myelocytes. There was, however, no typical leukemic infiltration, but an occasional island of erythropoiesis was seen. No mitotic figures were seen among the myeloid cells. In several periportal areas the connective-tissue stroma was increased and spread peripherally replacing parenchyma. Around the central veins there was, in some instances, a slight degree of fatty infiltration. There was no inflammatory reaction anywhere. The parenchyma was on the whole well preserved and, despite the congestion, the characteristic liver cords and lobules were distinctly seen. The gall-bladder was normal.

The thyroid gland, pancreas, gastrointestinal tract and pelvic organs showed engorged bloodvessels but were otherwise normal. The right kidney weighed 180 gm., the left 160 gm. They appeared normal. The sections showed no abnormalities nor evidence of leukemic infiltration. The adrenals were smaller than usual but were of normal shape and consistency. In one adrenal a small deep, brownish-red patch, which resembled a hemorrhage, was noted. Section of the adrenal glands showed several clusters of leukocytes composed of lymphocytes, plasma cells and young blast cells, possibly of the myeloid series. These groups of cells, situated in the medulla, were larger than those found in the liver and were more suggestive of a true leukemic infiltration. The bloodvessels were conspicuous owing to congestion.

The bone marrow from the femur, vertebræ, ribs and calvarium was hyperplastic and dull reddish-gray in color. On section (see photomicrograph) the bone marrow appeared congested. The bone spicules seen showed no degeneration nor defect in calcification. Only occasional fat cells were seen within the marrow. Numerous small clusters of cells with hyperchromatic nuclei and basic to eosinophilic cytoplasm representing areas of hematopoiesis were seen. Likewise there were numerous areas of myelocytes and their derivatives. Megakaryocytes were numerous and active. Eosinophils appeared to be present in greater number than in normal bone marrow. The histologic appearance was, however, not that which is usually found in leukemia, in that the myelocyte element was not excessive. To what extent, if any, the changes in the bone marrow have been influenced by phenylhydrazin and radiation is difficult to say.

The pathology of the brain was that of a diffuse hemorrhage into the subarachnoid space. The extravasation of blood was largely confined to the superior, lateral and medial aspects of the lobes of the cerebrum and cerebellum. There were no visible thrombi in the vessels. Most of the blood was found in the sulci and was of such diffuse distribution that it probably originated from the capillary bed. The arteries showed less sclerosis than

is generally found at the patient's age. There was a slight pressure cone on the inferior surface of the cerebellum. The ventricles were not dilated and they contained no blood in their cavities. The pons, medulla and cerebellum showed no hemorrhages into their substance. There were degenerative changes in many of the nerve cells of the cortex, but none were noted in the fiber tracts. The spinal cord showed massive hemorrhage into the subarachnoid space, similar to the brain, associated with which was edema and congestion of the cord and membranes.

Summary of Pathology. The pathologic picture was that of polycythemia with a terminal generalized subarachnoid hemorrhage of the brain and cord. The spleen weighed 1220 gm. and showed old infarcts, congestion, fibrosis and infiltration with abnormal cells. The bone marrow showed slightly greater hematopoiesis than normal, but there was no leukemic response on the part of the marrow. None of the organs, except possibly the adrenals, showed cellular infiltration suggestive of leukemia.

CASE 2.—F. P. (P. B. B. H. Med. 4444). A female, aged 66 years, entered the hospital complaining of a mass in the abdomen of 3 years' duration. Physical examination showed the general appearance suggestive of polycythemia, and an enormous spleen which filled the entire left side of the abdomen. Four blood examinations revealed an average red count of 4,903,000 (4,760,000 to 5,550,000) hemoglobin of 133 per cent (132 to 138) (NOTE.—These excessively high hemoglobin figures are questioned.) White count of 20,600 (20,100 to 21,700) and differential of polymorphonuclears, 81 per cent; lymphocytes, 1 per cent; monocytes, 14 per cent; eosinophils, 2 per cent, and basophils, 2 per cent. The smear showed 1 megaloblast and slight anisocytosis and poikilocytosis. The basal metabolic rate was 50 per cent above normal. Following discharge the patient lived 2 years. During the first year she received 22 Roentgen ray treatments over the spleen. Despite this treatment her red cell count mounted progressively, reaching a peak of 13,064,000 nine months after discharge. The hemoglobin varied between 95 and 132 per cent. The white count fluctuated between 12,000 and 24,000. Toward the end of the first year after discharge the red count began falling rapidly. Roentgen ray treatment was stopped but the red count continued to decline. The white cell count remained between 14,000 and 27,000. The differential count continued to show only a few myelocytes. Before death the counts were: red cells, 3,580,000; leukocytes, 28,000; hemoglobin, 68 per cent; differential cell count: polymorphonuclears, 37 per cent; young polymorphonuclears, 30 per cent; lymphocytes, 18 per cent; large monocytes, 8 per cent; basophils, 2 per cent; myelocytes, 5 per cent. Autopsy revealed typical myelogenous leukemia.

CASE 3.—(P. B. B. H. Med. 21587). A male, aged 37 years, entered the hospital because of swelling of the abdomen and pain in the left upper quadrant of 3 years' duration. Physical examination revealed emaciation, shifting dullness in the abdomen and the spleen 3 cm. below the costal margin. There was no erythema or cyanosis. Blood studies revealed hemoglobin, 126 per cent; red count, 6,430,000; white count, 49,000 with a differential of polymorphonuclears, 88 per cent; lymphocytes, 4 per cent; myelocytes, 8 per cent. The smear showed normoblasts and many immature leukocytes. The patient died 3 days after admission. Autopsy was not obtained.

CASE 4.—J. M. (P. B. B. H. Med. 7241). A white male, aged 61 years, entered the hospital because of a sense of pressure and swelling in the region of the spleen of 4 months' duration. Physical examinationed shown an erythematous appearance to the face and generalized adenopathy with several small firm nodes in the anterior axillary line. The spleen was 15 cm. below the costal margin. Before treatment the hemoglobin ranged between 95 and 125 per cent, averaging 107 per cent, the red count was 5,886,000

and the white count was 26,000. The differential showed 71 per cent polymorphonuclears, 6 per cent lymphocytes, 7 per cent monocytes, 11 per cent eosinophils, 5 per cent mast cells. The smear showed slight achromia, anisocytosis and a few macrocytes. Biopsy on one of the lymph nodes was reported as lymphoblastoma.

After receiving 78,688 millicuries of radiation over the splenic area, the spleen decreased slightly in size but the liver increased to 10 cm. below the costal margin. Under treatment, myelocytes began to appear in the blood stream. The hemoglobin fell to 80 per cent, the red cells rose to 7,360,000 and the white blood cells rose to 38,000. The average differential showed 62 per cent polymorphonuclears, 12 per cent lymphocytes, 4.3 per cent monocytes, 14.8 per cent eosinophils, 0.5 per cent basophils, and 5.5 per cent myelocytes. The patient died 3 months after admission. Before death the white count had fallen to 15,000 and the red count to 3,750,000. Despite the biopsy report of lymphoblastoma, a final diagnosis of chronic myelogenous leukemia was recorded.

CASE 5.—M. J. C. (P. B. B. H. Med. 37743), aged 45 years, white, single, Irish-American, woolsorter, entered the hospital because of severe abdominal pain of 4 days' duration. For 12 years the patient has had vague, intermittent, dragging upper abdominal pain relieved by soft and bland foods. Two years before admission, Roentgen ray examination showed a duodenal ulcer. Four days before admission the pain became unbearably sharp and aggravated by exertion.

Physical examination showed the appearance of the skin and mucous membranes characteristic of polycythemia. There was increased resistance and tenderness in the left upper quadrant of the abdomen where a firm mass extending three fingers' breadth below the costal margin was felt. The patient's temperature was elevated to 100° F.

Laboratory Studies. Roentgen ray studies of the gastrointestinal tract showed the stomach displaced to the right with pressure narrowing of the fundus, possibly due to an enlarged spleen. The duodenum showed a constant deformity suggestive of an ulcer. The urine and stool examinations gave negative findings. The Wassermann, Hinton and modified Hinton blood tests were negative. Gastric analysis after the Ewald test meal showed a maximum free acidity of 100 units of 0.1-N sodium hydroxid and a maximum total acidity of 130 units. The blood sugar was 101 mg. per cent., blood urea nitrogen, 21 mg. per cent; blood uric acid, 3.2 mg. per cent (old method); blood uric acid, 2.8 mg. per cent (new method); blood creatinin, 1.4 mg. per cent; blood phosphate, 4.3 mg. per cent; total proteins, 7.5 per cent; blood albumin, 4.4 per cent; blood globulin, 2.1 per cent; blood calcium, 10.6 per cent. Hematocrit cells, 61.2 per cent, plasma, 38.8 per cent; individual red blood cell volume 6.2 by 10^{-11} cc. The reticulocytes varied between 0.8 per cent and 1.6 per cent. Red cell fragility gave beginning hemolysis in a 0.38 per cent sodium chlorid solution. Hemolysis was not complete in a 0.28 per cent solution after 2 hours. The icteric index was 6. The bleeding time by the method of Duke was 1 minute and 30 seconds, the clotting time (capillary method), 2 minutes and 15 seconds. Platelet count was 320,000 (Wright and Kinnicutt method). Blood counts were as follows:

October 2: Hemoglobin (?) 75 per cent (Tallqvist); red cells, 7,700,000; leukocytes, 31,700. Differential: polymorphonuclears, 86 per cent; lymphocytes, 8 per cent; eosinophils, 3 per cent; myelocytes, 3 per cent. Red cells showed slight achromia. Platelets normal.

October 3: Hemoglobin, 158 per cent (Sahli); differential: polymorphonuclears, 88 per cent; lymphocytes, 5 per cent; large monocytes, 1 per cent; eosinophils, 1 per cent; basophils, 1 per cent; myelocytes, 4 per cent. Red cells normal.

October 5: Red cells, 8,610,000; leukocytes, 31,500.

October 8: Hemoglobin, 155 per cent (Sahli); red cells, 9,400,000; leukocytes, 28,500.

October 11: Red cells, 8,550,000; leukocytes, 45,500. Differential: polymorphonuclears, 91 per cent; lymphocytes, 5 per cent; large monocytes, 2 per cent; eosinophils, 1 per cent; basophils, 1 per cent. Red cells normal.

October 17: Leukocytes, 44,000.

Clinical Course. The patient was placed on the Sippy régime. He continued to vomit and complain of increasing left upper quadrant pain. The possibility of a splenic infarct, or an infectious process was considered. On the sixteenth day after admission the pain became increasingly severe, the upper portion of the abdomen became tense and gave an impression of boggy fullness. The patient vomited bright red blood several times. There was marked vasomotor collapse and within a few hours the patient died. The course of events suggested the possibility of thrombosis of the splenic and portal veins with gastric hemorrhage as the cause of death.

Comment. A survey of the cases in the literature which present a combination of elements of both diseases suggests that:

1. In those cases which terminate as myelogenous leukemia, the disease generally starts with a phase suggestive of polycythemia. This polycythemia phase gradually disappears as the leukemic characteristics appear and grow more pronounced. Indeed, Naegeli[4] believes that there is an initial polycythemia in the early stage of all cases of myelogenous leukemia.

2. In the cases of true erythremia the appearance of a marked leukocytosis with immature myeloid cells in the blood stream is generally a late manifestation and is evidence of a more profound disorganization of bone-marrow activity. This concept has been expressed by Minot[2] and Harrop.[3]

3. There may be a few cases which start out with the picture of myelogenous leukemia and undergo a progressive transition into true erythremia. Gheron,[3,4] and Winter[5] have reported such cases.

4. A case presenting the composite picture of myelogenous leukemia and polycythemia, or phases of each, is more than likely to be leukemia than erythremia. Thus, of 33 cases reviewed in the literature, 12 turned out to be leukemia and 5 erythremia. The remaining cases could not be classified, principally because they did not include postmortem examination. There were a few cases in which autopsy showed the presence of characteristics of both diseases, making differentiation impossible.

It is noteworthy that our patient died suddenly during the course of Roentgen ray treatment over the spleen. The question naturally arises as to whether there was any relationship between radiation and the sudden death. Horstrup[4] points out the advisability of considering those patients with the combined picture as potentially poor risks for radiation. He cites only 1 case from the literature that was definitely improved by radiation over the spleen. Inasmuch as the disease runs a fatal course, often terminating suddenly,

and the appearance of immature myelocytic cells in the blood stream generally is a late manifestation in polycythemia, it is difficult to determine whether radiation actually hastens the end in this combined group. However, it is a possibility worth further consideration.

Summary. A case of erythremia presenting a marked leukocytosis, myelocytes in the blood stream, a huge spleen, and terminating fatally following Roentgen ray radiation therapy over the spleen, is reported with postmortem findings. Four similar cases appearing in the hospital records are reviewed briefly. A classification of cases having the combined picture of polycythemia and leukemia is suggested.

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PREGNANCY IN THE COURSE OF LEUKEMIA.

A Case Report.

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The number of reported cases of leukemia complicating pregnancy and of pregnancy occurring during the course of leukemia is small.[1,2] Because of this fact; because of the lack of unanimity of opinion regarding the transmissibility of the disease to the child;[1,3] because of the fact that pregnancy allowed to proceed to term is supposed to aggravate the leukemia and anticipate the fatal outcome;[4] and because of the difference of opinion regarding the effect of deep radiation therapy on the function of the ovaries,[5,6,7,8] we wish to report a normal pregnancy and delivery of a normal child occurring in a case of chronic myelogenous leukemia.

Case Report. R. B., female, white, nativity United States, aged 26 years, married, was admitted, October 22, 1928, and discharged, December 12, 1928.

Family History. Irrelevant.

Past History. Menstruation began at the age of 12 years; was of the 28-day type, not painful and apparently not excessive. The patient was married at the age of 18 years. She was delivered of a normal baby boy 9 months and 2 weeks from the date of her marriage. This pregnancy was characterized by the fact that nausea and vomiting began early in its course, that they were severe and that they persisted almost to up to the date of delivery. Menstruation occurred 5 months after this delivery. Two years and 9 months later the patient was delivered of a second normal baby boy. She had persistent, severe nausea, vomiting and headache during pregnancy. In the interval between these pregnancies, however, the patient felt perfectly well and carried on her household duties without difficulty. Menstruation recurred 7 months after this delivery.

Present Illness. About 15 months before admission the patient noticed that she tired easily. Progressive, severe and generalized weakness followed with head noises, headache and dizziness and blurring of vision. Her appetite became poor and the ingestion of food was accompanied by epigastric discomfort. The attacks of abdominal distress gradually became more frequent and protracted, so that they were present even when fasting. Later she complained of a diffuse swelling in the region of the thyroid gland.[4] Subsequently shortness of breath developed which was aggravated by exercise and by the taking of food. About this time and quite by accident she felt a large mass (spleen) in the left upper abdomen. Bleeding from the gums and crops of purpuric spots occurred at first irregularly, but later rather frequently. Weakness, shortness of breath, abdominal distention and dragging sensation in the left upper abdomen finally became so severe that she applied for admission to the hospital for relief.

Physical Examination. There was diffuse, uniform enlargement of the thyroid; the gums were tender and bled easily on pressure; the lungs were essentially negative; the heart showed a soft, short systolic blow over the mitral area; the liver was enlarged about 1 inch below the free costal margin, smooth and not tender; the spleen was markedly enlarged, extending almost to the midline anteriorly and inferiorly to the level of the iliac crest; the inguinal and axillary lymph nodes were palpably enlarged, discrete and not tender. A few purpuric lesions were scattered over the skin of the lower extremities, but there were no leukemic nodules or diffuse leukemic infiltration of the skin. The neurologic status, excepting slight impairment of the vibratory sense in the toes, was normal.

Laboratory Data. Hemoglobin, 69 per cent, or 9.35 gm. (Dare); red cell count, 4.52 million; color index, 0.77; reticulocytes, 5 per cent; white cell count, 122,800. Differential count: Myeloblasts, 0; premyelocytes, 6 per cent; myelocytes, 12 per cent; metamyelocyte (I), 10 per cent; metamyelocytes (II), 18 per cent; neutrophils, 46 per cent; lymphocytes, 5 per cent; monocytes, 1 per cent; eosinophils, 2 per cent; basophils, 0. The platelets were numerous. Examination of the red cells in the stained film showed moderate qualitative changes. Coagulation time (Lee and White), 7 minutes; clot retraction good; bleeding time (Duke), 1 minute. Fragility of the red cells: Patient: Beginning hemolysis, 0.5 per cent sodium chlorid; complete hemolysis, 0.28 per cent sodium chlorid. Control: Beginning hemolysis, 0.44 per cent sodium chlorid; complete hemolysis, 0.32 per cent sodium chlorid. Van den Bergh: Immediate direct reaction, negative; indirect reaction, weakly positive. Icterus index, 9. The blood Wassermann test was negative (alcohol and cholesterin antigens). The blood sugar was 70 mg. per 100 cc. Urea nitrogen, 14.5 mg. per 100 cc. The

TABLE 1.—WHITE AND DIFFERENTIAL FORMULÆ AND RADIATION THERAPY DURING PERIOD OF HOSPITALIZATION, OCTOBER 22, 1928, TO DECEMBER 12, 1928.

Date, 1928.	Erythrocytes.	Hemoglobin (Dare), per cent.	Grams.	Color index.	Reticulocytes, per cent.	Leukocytes, thousands.	Myeloblasts.	Premyelocytes.	Myelocytes.	Metamyelocytes (I).	Metamyelocytes (II).	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Radiation treatment.
Nov. 2 . . .	4.45	67	9.1	0.75	4.5	125.0	3	4	20	10	14	41	2	2	3	1	X A.S.
Nov. 9 . . .	4.10	66	9.0	0.80	5.0	83.8	2	5	14	11	16	45	2	1	2	2	X A.S.
Nov. 16 . . .	3.99	53	7.2	0.70	4.8	102.6	0	6	13	13	18	47	1	0	2	0	X A.S.
Nov. 27 . . .	4.33	52	7.1	0.60	5.8	98.0	0	7	14	5	13	52	3	3	1	2	X A.S.
Dec. 1 . . .	4.26	..	..	..	3.5	80.6	0	7	9	3	9	62	2	5	1	2	
Dec. 4 . . .	4.47	61	8.3	0.70	5.8	68.4	0	6	7	2	6	71	5	1	2	0	X A.S.
Dec. 10 . . .	5.25	62	8.4	0.60	5.0	40.0	0	5	9	9	13	54	2	4	1	3	

X A.S. = Deep radiation treatment over anterior spleen.
X P.S. = Deep radiation treatment over posterior spleen.
Details of radiation treatments are given under Treatment and Course in text.

urine was essentially normal. Bence-Jones bodies were not demonstrated. Urinary urobilinogen was normal throughout entire period of observation. The feces were negative for ova, parasites, pus, blood, excess mucus and Charcot-Leyden crystals. Fractional gastric analysis (Ewald test meal) at 15-minute intervals up to 105 minutes gave normal values for free hydrochloric acid and total acidity. Basal metabolic rate was +12.5 per cent. (Roth-Benedict apparatus — Aub-Du Bois standards.) Gastrointestinal fluoroscopy showed a normal esophagus, stomach and duodenum. The electrocardiogram showed sinus tachycardia. Temperature, 100° F.; pulse, 80; respiration, 22; blood pressure, 111 mm. of mercury systolic and 74 mm. of mercury diastolic; weight, 123 pounds.

Treatment and Course. Deep Roentgen ray radiation therapy was started 11 days after admission, that is, on November 2. The details of the dosage were as follows: Size of area, 9 by 12 cm.; milliamperes, 4; K-V, 200; filter, Cu. 0.5 mm.; Al., 1 mm.; distance, 30 cm.; per cent erythema, 25; time, 7 minutes. The blood picture (Table 1) showed a rapid reduction in the total white cell count in response to the 5 deep radiation treatments given between November 2 and December 10, 1928. The red cells were not adversely affected. It is interesting to note that during this period of treatment the percentage of reticulocytes was always slightly above normal.

Subjectively and objectively the response to deep radiation therapy was as striking and satisfactory as was the response hematologically. The outstanding feature of the clinical response, as was to be expected, was the strikingly rapid and complete reduction in the size of the spleen. Following the Roentgen ray therapy the patient experienced what might be regarded as postradiation reaction, which manifested itself as nausea, "hot flashes," chilly sensations along the spine and profuse perspiration of the palms.

She was discharged to the return blood clinic on December 12, 1928. In Table 2 are given the dates of the return visits with the white cell counts and radiation treatments. During the first three visits to the return clinic, December 19 and 26, 1928, and January 9, 1929, the total white counts were 30,000, 26,400 and 11,400 respectively. Radiation therapy was given on the first two return visits and none on the third. The patient did not appear again at the return clinic for a period of about 9 months, that is, September 26, 1929, when her white count was found to be 130,200. The response to Roentgen ray therapy was quite rapid, as can be seen from

TABLE 2.—TOTAL WHITE CELL COUNTS AND DEEP RADIATION TREATMENTS WITH THEIR DATES, FROM DECEMBER 19, 1928, TO DECEMBER 19, 1929.

Date, 1928.	White blood cells.	Treatment.
Dec. 19	30,000	X P.S.
Dec. 26	26,400	X P.S.
1929.		
Jan. 9	11,400	None
Sept. 26	130,200	X A.S.
Sept. 30	86,700	X A.S.
Oct. 2	91,200	X A.S.
Oct. 7	72,900	X A.S.
Oct. 9	71,700	X P.S.
Oct. 14	50,600	X P.S.
Oct. 16	43,600	X P.S.
Oct. 24	29,600	None
Oct. 31	16,700	None
Nov. 21	5,100	None
Dec. 19	9,400	None

X A.S. = Deep radiation treatment over anterior spleen.
X P.S. = Deep radiation treatment over posterior spleen.
Details of radiation treatments are given under Treatment and Course in text.

TABLE 3.—TOTAL WHITE CELL COUNTS, DIFFERENTIAL FORMULÆ, HEMOGLOBIN, RED CELL, COLOR INDEX AND RETICULOCYTE DETERMINATIONS. DEEP RADIATION TREATMENTS AND THEIR DATES, FROM JANUARY 16, 1930, TO MARCH 21, 1931.

Date.	Total white blood cells, thousands.	Myeloblasts.	Premyelocytes.	Myelocytes.	Metamyelocytes (I).	Metamyelocytes (II).	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Plasma cells.	Radiation treatment.	Hemoglobin (Dare), per cent.	Grams.	Erythrocytes.	Color index.	Reticulocytes, per cent.
1930.																		
Jan. 16	9.9	0	1	2	0	4	83	4	2	2	2	0	None	67.0	9.1	5.03	0.67	3.6
Feb. 13	12.4	..	..	..	..	..	..	..	..	..	..	..	None					
Mar. 13	14.6	..	..	..	..	..	..	..	..	..	..	..	None					
Mar. 18	15.7	..	..	..	..	..	..	..	..	..	..	..	None					
April 15	23.8	..	..	..	..	..	..	..	..	..	..	..	None					
April 23	21.5	0	3	5	2	10	67	5	2	3	2	1	None					
July 18	39.3	..	..	..	..	..	..	..	..	..	..	..	None					
July 30	46.6	..	..	..	..	..	..	..	..	..	..	..	None					
Sept. 12	66.4	..	..	..	..	..	..	..	..	..	..	..	None					
Sept. 18	70.3	1	8	6	14	14	47	3	4	1	2	0	None					
Oct. 21	78.6	..	..	..	..	..	..	..	..	..	..	..	None					
Nov. 19	100.4	..	..	..	..	..	..	..	..	..	..	..	A.S.					
Nov. 26	112.6	0	12	14	7	33	32	0	1	1	0	0	A.S.					
Dec. 5	80.6	..	..	..	..	..	..	..	..	..	..	..	A.S.					
Dec. 9	109.6	..	..	..	..	..	..	..	..	..	..	..	A.S.					
Dec. 12	103.8	..	..	..	..	..	..	..	..	..	..	..	P.S.					
Dec. 16	77.6	1	13	10	7	19	41	1	2	4	2	0	P.S.					
Dec. 19	80.0	..	..	..	..	..	..	..	..	..	..	..	P.S.					
Dec. 22	97.8	..	..	..	..	..	..	..	..	..	..	..	P.S.					
Dec. 29	36.5	..	..	..	..	..	..	..	..	..	..	..	None					
1931.																		
Jan. 16	15.0	..	..	..	..	..	..	..	..	..	..	..	None					
Feb. 19	9.0	..	..	..	..	..	..	..	..	..	..	..	None					
Mar. 3	13.0	..	..	..	..	..	..	..	..	..	..	..	None					
Mar. 21	15.2	0	0	8	1	2	77	6	3	1	1	1	None	94.6	16.0	5.05	0.94	2.0

Pregnancy.

X A.S. = Deep radiation treatment over anterior spleen.
X P.S. = Deep radiation treatment over posterior spleen.

Table 2. If one compares the data in Tables 1 and 2 the following are apparent: that the number of treatments was not large; that the reduction in the total number of white cells was rapid; that the treatments were given only over the anterior and posterior spleen.

Pregnancy and Subsequent Course. The patient had her last menstrual period in December, 1929. In January, 1930, she missed her menstrual period and began to complain of symptoms that from previous experience she associated with pregnancy, as follows: anorexia, nausea and vomiting. In April, 1930, there were definite physical evidences of pregnancy. In May, because of persistent vaginal bleeding, she was admitted to the hospital, where a diagnosis of threatened abortion was made. With rest in bed and with the use of sedatives, the bleeding stopped and the patient was discharged at the end of a week. On September 13 the patient went into labor spontaneously and was delivered of a male child weighing 7 pounds 10 ounces. The labor was entirely uncomplicated and of comparatively short duration, less than 24 hours elapsing from the time of beginning premonitory symptoms until delivery. During the period of gestation the patient complained of anorexia, nausea, vomiting, feeling of fullness in the abdomen, especially in the left upper quadrant, the appearance of crops of purpura, especially over the lower extremities and transient attacks of numbness and tingling of the fingers and toes. Excepting the external manifestations of pregnancy, the patient's physical appearance was but little altered from that presented prior to the onset of pregnancy.

From an examination of Table 3 it can be seen that the total white count increased during the period of pregnancy to a level of about 70,000 at the time of delivery and the differential formulæ also changed in that there occurred an increase in the number of less differentiated granulocytic cells. The white count continued to rise after delivery, but here again a short course of deep radiation treatments over the anterior and posterior spleen was followed by a striking and prompt decrease in the total number of white cells. During the period extending from January 16, 1930, that is, the date of the onset of pregnancy, to March 21, 1931, the date of this writing, there have been no striking qualitative or quantitative variations in the red cell picture.

Comment. From a study of Tables 1, 2 and 3, it is quite evident after radiation that the total leukocyte count never reached a very high level. At no time during the course of the disease could any evidence be adduced from the clinical findings and from a study of the differential formulæ that a chronic form of the disease was becoming acute. The striking response of the white cells to deep radiation therapy is quite apparent and noteworthy. There were three series of deep radiation treatments of seven, seven and eight treatments respectively with results as previously given.

There is no evidence that the pregnancy aggravated the course of the leukemia in this patient. As far as can be determined the child is perfectly normal, hematologically and physically. In the course of the deep radiation therapy, no attempt was made to radiate the ovaries, the treatments being confined to the anterior and posterior spleen. Because of this fact, there does not seem to be any valid reason for this patient's not becoming pregnant if one excepts the existence of leukemia as preventing the occurrence of pregnancy.

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THE INCIDENCE AND SITUATION OF MYOCARDIAL INFARCTION IN ONE THOUSAND CONSECUTIVE POSTMORTEM EXAMINATIONS.*

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Coronary occlusion and myocardial infarction have been the subject of many clinical, electrocardiographic and pathologic studies in recent years. Communications dealing with the pathologic details have been relatively few and particularly lacking in details relative to the incidence and situation of infarction in a large series of cases.

Benson and Hunter found 200 cases of obstructive disease of the coronary arteries in 1750 postmortem examinations. However, they were able to demonstrate acute or chronic infarction in only 76 of these cases, an incidence of infarction of 4.3 per cent. In 54 additional subjects (3 per cent) fresh thrombi were present in the coronary arteries, without infarction or aneurysm having been produced. They did not give the details of the situation of the infarction. Parkinson and Bedford observed that the main branch of the left coronary artery was occluded in 3 cases, the anterior descending branch in 24, the circumflex branch in 10 and the right coronary artery in 18. They did not give the details of the situation of infarction in their cases. Other reports[7,8,13] contain valuable observations on the pathology of coronary occlusion, but the authors did not pay particular attention to incidence and situation of infarction nor did they report the situation of the obstruction in the coronary arteries.

In undertaking any study of myocardial infarction, the normal or

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usual distribution of the coronary arteries must be known. The recent investigations of Whitten, with his celluloid corrosion methods of demonstrating the cardiac circulation, have given the necessary information. Utilization of these preparations has been made in Figs. 1, 2 and 3.

As previously has been pointed out by Parkinson and Bedford and by Barnes and Whitten, myocardial infarction is almost completely confined to the left ventricle. It has not been emphasized before, however, that infarction in the left ventricle is found chiefly in 3 situations due to the distribution of the 3 main arterial branches

FIG. 1.—*MI*, Region partially or completely involved by myocardial infarction in 28 cases. In every instance the anterior descending branch of the left coronary artery supplied this portion of the heart. *RV*, right ventricle; *LV*, left ventricle; *AD*, anterior descending branch of the left coronary artery; *C*, circumflex branch of the left coronary artery; *RC*, right coronary artery; *VV*, veins. Region between *U*—*U* and *O*—*O*, roughly corresponds to the portion of the heart supplied by the anterior descending branch of the left coronary artery.

of the right and left coronary arteries responsible for its blood supply. Inasmuch as the several infarctions observed in this series conform more or less closely to 1 or more of these typical situations it is necessary to describe each in some detail.*

One type may be described as involving the apex and anterior portion of the left ventricle and is almost always due to occlusion of the anterior descending branch of the left coronary artery, or more rarely to occlusion of the main trunk of the left coronary vessel.

* For greater details regarding the types of infarction and their relation to blood supply the reader is referred to Whitten's observation.

The infarction usually occurs at considerable distance from the site of occlusion, so that the apex is almost invariably involved. With it a portion of the anterior $\frac{1}{3}$ to $\frac{1}{4}$ of the left ventricle is involved, extending upward a variable distance toward the base, rarely reaching a point more than $\frac{2}{3}$ to $\frac{3}{4}$ of the distance from the apex to the base. The adjacent interventricular septum is involved but the neighboring portion of the right ventricle almost always escapes serious injury. This will be referred to as the anterior apical type of infarction.

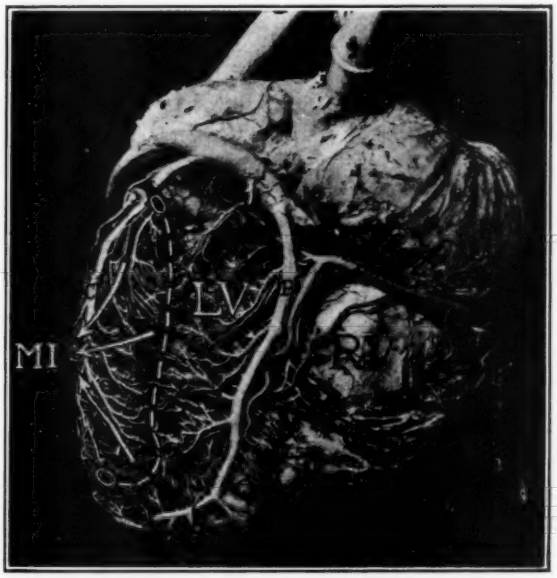

FIG. 2.—*MI*, Region partially or completely involved by myocardial infarction in 8 cases. In every instance the circumflex branch of the left coronary artery supplied this portion of the heart. *RV*, right ventricle; *LV*, left ventricle; *P*, posterior descending vein roughly marking the division between the right and left ventricles; *RC*, right coronary artery; *C*, circumflex branch of the left coronary artery; *O—O*, line roughly separating the portion of the left ventricle supplied by the circumflex branch of the left coronary artery from that supplied by the right coronary artery.

Infarction of the midventricle constitutes a second typical situation of infarction of the left ventricle. This infarction characteristically involves the obtuse margin of the left ventricle about midway between the base and apex, although it may occur at the base and occasionally well down toward the apex. This usually results from occlusion of the circumflex branch of the left coronary artery. The term midventricular infarct will be used when referring to an infarct in this situation in the left ventricle.

A third very common site of infarction in the left ventricle, and one that has been frequently overlooked, is the posterior basal

portion of the left ventricle. This usually involves the basal three-fifths of the posterior portion of the left ventricle, the adjacent portion of the interventricular septum, and very rarely a small border of the adjacent right ventricle. This usually results from occlusion of a branch or of the main trunk of the right coronary artery, although in an occasional case the circumflex branch of the left coronary artery is the site of occlusion. Variations of the region of infarction here depend on variations in blood supply, and occasionally the infarct at the posterior part of the base may

FIG. 3.—*MI*, Region partially or completely involved by myocardial infarction in 24 cases. This portion of the heart was supplied by the right coronary artery in 17 cases, by the circumflex branch of the left coronary artery in 5 cases, and by both the right coronary artery and the circumflex branch of the left coronary artery in 2 cases. *RV*, right ventricle; *LV*, left ventricle; *RC*, right coronary artery; *P*, posterior descending vein; *C*, circumflex branch of the left coronary artery; *O—O*, line roughly separating the portions of the left ventricle supplied by the circumflex branch of the left coronary artery from that supplied by the right coronary artery.

extend to the obtuse margin, to the apex, or to both. Infarctions in this portion of the left ventricle will be spoken of as posterior basal infarctions.

This study was undertaken to determine, as accurately as possible, the incidence and situation of infarction. The material was obtained from 1000 consecutive postmortem examinations performed at The Mayo Clinic. It included all ages and both sexes, and no cases were excluded on any ground.

In the 1000 consecutive postmortem examinations there were

49 hearts in which there was gross evidence of myocardial infarction, an incidence of 4.9 per cent. Forty of the subjects were men and 9 were women.

The infarctions described here were recognized by gross methods, either by inspection or palpation or both. The infarcts encountered were acute, healed acute, or chronic. Acute myocardial infarction has definite pathologic characteristics and needs no discussion. We have classified infarcts as healed acute when they were localized, when they led to more or less complete replacement of the ventricular wall by fibrous tissue, and whether or not there was an organized thrombus of the endocardium corresponding to the region of infarction. In a certain number of cases the designation of healed acute infarction was strengthened by a previous history indicative of acute coronary occlusion. When we use the term "chronic infarction" we have reference to those cases in which the fibrous replacement is less complete and more patchy in its distribution than that seen in healing following acute infarction, although at times it may be impossible to distinguish the two types. We believe that chronic infarction results from the gradual, almost complete obliteration of the lumen of a coronary vessel which supplies a region that is involved. Cases in which chronic infarction was localized are included in the statistics regarding situation of infarction. In an occasional instance, chronic infarction is diffuse, tends to exist in the form of subendocardial fibrosis and involves the entire left ventricle more or less completely. It is not unusual for acute or healed acute infarction to be present in a left ventricle which is the seat of diffuse fibrosis of the chronic type.

Of the 49 infarctions, 47 had occurred among patients who had died at 40 years of age or more, an incidence of 6.86 per cent. Approximately 70 per cent of the infarctions had occurred among patients who were between the ages of 50 and 69 years when they died. The distribution of cases and the incidence of infarction by decades of life is given in Table 1.

TABLE 1.—DISTRIBUTION OF CASES AND INCIDENCE OF INFARCTION BY DECADES OF LIFE.

Age groups.	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Subjects examined (total 1000) . .	107	37	62	109	167	223	203	74	15	3
Infarction	0	1	0	1	6	18	17	5	0	1
Percentage of infarction	0.0	2.7	0.0	0.9	3.5	8.0	8.3	6.7	0.0	33.3

One patient had had a definite history of syphilis, and 1 a questionable history of it, but the Wassermann reaction of the blood of both had been negative. The Wassermann reaction of blood and

spinal fluid of 1 patient had been positive and there had been definite neurologic evidence of syphilis of the central nervous system.

The blood pressure of 42 patients had been recorded at the time of their admission. The systolic blood pressure of 8 patients had been more than 150 mm. of mercury and the diastolic pressure more than 100 mm. In 5 cases the systolic pressure had been less than 150 mm. and the diastolic more than 100 mm. In 18 cases the systolic pressure had been less than 150 mm. and the diastolic less than 100 mm.

Five patients had given histories of angina pectoris, or dyspnea, or both, preceding the history that was indicative of the first coronary occlusion. In 24 subjects with myocardial infarction there had been a definite history of coronary occlusion. Twelve of these patients had had multiple myocardial infarctions, 9 of whom had given histories of a second coronary occlusion.

As near as could be determined the myocardial infarction had been the cause of death in 18 cases, a contributing cause in 19 cases, a possible contributory cause in 7 cases, and in 5 cases it had played no appreciable part in causing death.

The electrocardiographic changes observed following coronary occlusion have been described.[2,6,9,11] Electrocardiograms had been taken in 35 of the cases in the group described here. In 11 cases of acute infarction the electrocardiograms had been characteristic of the situation of infarction according to the criteria presented by Barnes and Whitten.[3] In 19 cases of healed acute or chronic infarction electrocardiographic abnormalities that were not pathognomonic of infarction had been observed. These had included instances of significant *T* wave changes, bundle-branch block, auricular flutter, and auricular fibrillation. The lack of changes characteristic of infarction in this group is accounted for, in some cases, by the fact that the infarctions were ancient, and in some cases by the fact that the occurrence of bundle-branch block had obscured the electrocardiographic features that might have been indicative of myocardial infarction. The electrocardiograms of 5 patients had not revealed significant changes.

The weight of the hearts tended to exceed the average calculated weight for the sex and age of the patients. Seven hearts weighed between 300 and 400 gm.; 17, between 400 and 500 gm.; 12, between 500 and 600 gm.; 7, between 600 and 700 gm.; 5, between 700 and 800 gm., and 1 weighed 800 gm. It seems certain that any heart which weighs 500 gm. or more is hypertrophied and a little more than half of the hearts exceeded that weight. We look on this increased size of the heart as being a result of associated hypertension which has been shown to have been present in 24 of 42 patients in whose cases readings of blood pressure were obtained. On the other hand, coronary occlusion and myocardial infarction occurred in cases in which the hearts were of normal size and blood

pressure was normal. It must be emphasized therefore that neither hypertension nor cardiac hypertrophy is a necessary concomitant of coronary sclerosis or occlusion.

Acute or chronic disease of the pericardium related to myocardial infarction was observed in 11 of the 49 cases. This ratio, as indicative of the incidence of pericarditis in cases of myocardial infarction, may be a little too high; it was not always possible to be sure that a chronic adherent pericardium was a relic of acute pericarditis due to myocardial infarction.

Certain traditional conceptions as to the branches of the coronary arteries most prone to undergo acute occlusion and as to the predisposition of certain branches to develop coronary sclerosis have gained wide acceptance. The prevalent idea is that most acute occlusions occur in the anterior descending branch of the left coronary artery. This has led to the designation of this branch as "the artery of sudden death." Although it still exceeds other branches in the frequency of its acute occlusion, the preponderance of such an occurrence is not nearly so great as commonly has been supposed.

Table 2 shows that definite occlusion of the anterior descending branch of the left coronary artery was demonstrated in 18 cases; of the circumflex branch, in 7, and of the right coronary artery, or a branch, in 9. However, in those cases in which definite occlusion could not be found, the vessel or branch supplying the region of infarction was identified by careful dissection. Most of these vessels presented segments which were almost completely occluded, and in some organization and canalization of thrombi was apparent. A study of these vessels, which were identified by dissection, in relation to their distribution to the regions of infarction, shows that the anterior descending branch of the left coronary artery was responsible for cardiac infarction in 10 cases, the circumflex branch, in 10, and the right coronary artery, in 11. Combining the group in which arteries were definitely occluded with the group in which the offending artery was identified by dissection it is seen that the anterior descending branch of the left coronary artery was responsible for gross myocardial infarction in 28 instances, the circumflex branch, in 17, and the right coronary artery, in 20.

The greater apparent frequency with which thrombi are demonstrated in the anterior descending branch of the left coronary artery in comparison with the other branches which supply the left ventricle is probably due chiefly to circumstances. First, the anterior descending branch is studied more carefully by the average pathologist than is the circumflex branch and the right coronary artery. This is particularly true of the branches of the right coronary artery distributed to the left ventricle, for dissection of these branches is tedious and at times somewhat difficult. In the second place, longitudinal incision of the anterior descending branch without

TABLE 2.—SITUATION OF INFARCTION AND OCCLUSION.*

Case.	Situation of infarction in left ventricle.				Artery demonstrated to be occluded.			Artery to region of infarction when occlusion not demonstrated.		
					Left coronary.			Left coronary.		
	Anterior portion and apex.	Median ventricular portion	Posterior basal portion	Diffusely beneath endocardium	Anterior descending branch	Circumflex branch	Right coronary	Anterior descending branch	Circumflex branch	Right coronary
1	−	+	+	−	−	−	−	−	+	+
2	+	+	+	−	+	+	+	−	−	−
3	+	−	−	−	−	−	−	+	−	−
4	+	−	−	−	+	−	−	−	−	−
5	+	−	−	−	+	−	−	−	−	−
6	+	−	−	−	−	−	−	+	−	−
7	+	+	−	−	+	−	−	−	+	−
8	+	−	−	−	+	−	−	−	−	−
9	−	−	−	+	−	+	+	−	−	−
10	+	−	−	−	−	−	−	+	−	−
11	−	−	−	+	+	+	−	−	−	−
12	−	−	+	−	−	+	−	−	−	−
13	+	−	−	−	+	−	−	−	−	−
14	+	−	−	−	+	−	−	−	−	−
15	+	−	+	−	+	−	+	−	−	−
16	−	−	+	−	−	−	+	−	−	−
17	+	−	−	−	−	−	−	+	−	−
18	−	−	+	−	−	−	−	−	−	+
19	+	−	−	−	+	−	−	−	−	−
20	+	+	−	−	−	−	−	+	+	−
21	−	−	+	−	−	+	−	−	−	−
22	−	−	+	−	−	−	+	−	−	−
23	−	−	+	−	−	+	+	−	−	−
24	−	+	−	−	−	−	−	−	+	−
25	+	−	−	−	+	−	−	−	−	−
26	+	−	+	−	+	−	+	−	−	−
27	+	−	+	−	+	−	−	−	−	+
28	−	−	+	−	−	−	−	−	+	−
29	+	−	−	−	−	−	−	+	−	−
30	−	−	+	−	−	−	−	−	−	+
31	+	−	+	+	−	−	−	−	+	+
32	−	−	+	−	−	−	+	−	−	−
33	+	−	−	−	+	−	−	−	−	−
34	−	−	+	−	−	−	−	−	+	−
35	+	−	−	−	−	−	−	+	−	−
36	−	−	+	−	−	−	−	−	−	+
37	−	−	+	−	−	−	−	−	−	+
38	+	−	−	−	+	−	−	−	−	−
39	+	−	−	−	−	−	−	+	−	−
40	−	−	+	−	−	−	−	−	−	+
41	−	−	+	−	−	−	−	−	−	+
42	−	−	+	−	−	−	+	−	−	−
43	+	+	−	−	−	−	−	+	+	−
44	−	+	−	−	−	−	−	−	+	−
45	+	+	−	−	+	+	−	−	−	−
46	−	−	+	−	−	−	−	−	−	+
47	+	−	+	−	−	−	−	+	−	+
48	+	−	+	−	+	−	−	−	+	−
49	+	−	−	−	+	−	−	−	−	−
Total	28	8	24	3	18	7	9	10	10	11

* The sign + is equivalent to the word "yes"; the sign −, to the word "no" under each heading.

dislodging a thrombus is certainly technically easier than similar incision of the arclike and at times tortuous right coronary artery. More lively suspicion that there may be thrombi occluding the right coronary artery and the circumflex branch of the left coronary artery and more painstaking study of those vessels will increase greatly the frequency of discovery of thrombi occluding those vessels.

As a corollary to the erroneous idea that the anterior descending branch of the left coronary artery is the usual site of coronary occlusion is the conception that most myocardial infarction is found in the apex and adjacent anterior portion of the left ventricle and anterior interventricular septum. Our investigation shows that gross myocardial infarction is found practically as commonly in the posterior basal portion of the left ventricle as in the apex and anterior portion (Table 2; Figs. 1, 2 and 3).

An attempt was made to grade on a scale of 1 to 4 the degree of sclerosis present in the right and left coronary arteries. We were under the impression that coronary sclerosis on the average was much more pronounced in the left coronary artery as compared with the right coronary artery. Our observations gave very little support to that idea. In 36 cases the degree of coronary sclerosis was estimated to be the same in the right and left coronary arteries. In 7 cases the sclerosis present in the left coronary artery was estimated to exceed that in the right by 1 point on our scale, in 3 cases, by 2 points, and in 1 case, by 3 points. In 2 instances the sclerosis of the right coronary artery was estimated to be greater than that in the left.

Furthermore, the frequency with which gross myocardial infarction occurs in the distribution of the right and left coronary arteries is probably a good index of the degree of sclerosis existent in those vessels. If we compare the number of infarctions observed in the region supplied by the right coronary artery with that observed in the region supplied by the anterior descending branch of the left coronary artery (Table 2) we do not find a great discrepancy.

Comment. It has become increasingly apparent that coronary thrombosis with myocardial infarction is a common occurrence in the human heart. The fact that in 6.8 per cent of subjects more than 40 years of age examined in a series of 1000 consecutive postmortem examinations, gross more or less localized infarction was found and that in 9 subjects 2 or more distinct infarctions were found, gives a conception of the incidence of this lesion. Seventy per cent of the cardiac infarctions were found among patients between the ages of 50 and 69 years.

This study serves to correct the impression that an overwhelming majority of cardiac infarctions occurs as results of occlusion of the anterior descending branch of the left coronary artery. It is no longer justifiable to designate the anterior descending branch as "the artery of coronary occlusion."

Furthermore, localized infarction is to be observed practically as frequently in the posterior basal portion of the left ventricle as it is in the apex and adjacent anterior portion of the left ventricle. It is important to point out that infarction in the posterior basal portion of the left ventricle often will be overlooked by the pathologist unless an incision through the left ventricle is made parallel with, and closely adjacent to, the posterior interventricular septum, extending from the apex to the mitral ring.

Barnes and Whitten described electrocardiographic changes by means of which it was possible to predict whether myocardial infarction would be found at necropsy to have involved the apex and anterior portion or the posterior basal portion of the left ventricle. The types of electrocardiographic changes characteristic of infarction in one and in the other of these regions were observed with equal frequency by Parkinson and Bedford. They felt that this equal frequency of occurrence of the 2 types were out of keeping with their observation that occlusion of the left coronary artery was twice as common as was occlusion of the right coronary artery. However, the circumflex branch of the left coronary artery fairly commonly supplies the posterior basal portion of the left ventricle. As a result of this fact, infarction in the posterior basal portion of the left ventricle may result from occlusion of the circumflex branch of the left coronary artery as well as from occlusion of the right coronary artery. Our study shows that cardiac infarction occurs in the posterior basal portion and in the anterior and apical portion of the left ventricle with approximately equal frequency. Thus Parkinson and Bedford's observation of the equal incidence of electrocardiographic changes pointing to infarction in the anterior and apical portion of the left ventricle on the one hand and pointing to infarction of its posterior basal portion on the other, is in harmony with our observations and supports rather than detracts from the localizing value of the electrocardiographic changes described by Barnes and Whitten.

Summary. In 1000 unselected consecutive postmortem examinations more or less localized myocardial infarction was recognized grossly in 49 subjects (4.9 per cent).

Of 685 of these subjects, 40 years of age or more, myocardial infarction was observed in 47 (6.86 per cent).

A majority of the subjects who had sustained myocardial infarction had had associated hypertension, as judged by the cardiac weights and the records of blood pressure.

Notable preponderance of arteriosclerosis in the left coronary artery over that found in the right was not observed in the hearts in which evidence of infarction was found.

Gross myocardial infarction resulting from coronary occlusion was practically confined to the left ventricle.

Myocardial infarction was observed in the posterior basal portion

of the left ventricle in 24 instances as compared with 28 instances in which it involved the apex and anterior portion. More careful pathologic study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region be not overlooked.

In 28 instances infarction occurred in the region supplied by the anterior descending branch of the left coronary artery, as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. The designation of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion" is no longer justifiable.

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STUDIES IN COMPLETE HEART BLOCK: II. A CLINICAL ANALYSIS OF 43 CASES.

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The discovery of complete auriculoventricular heart block is ordinarily considered of serious significance to the individual in whom it is found, even though he shows no symptoms or signs of heart failure. Textbook descriptions of the condition emphasize

its gravity and usually state that sudden death is not infrequent. Recently, however, it has come to be recognized that heart block may occasionally exist for many years without seriously affecting the health of the subject. Thus, Lewis[1] states that heart block *per se* does not kill and that although it is usually a sign of serious and often progressive myocardial damage, it may exist for some time, especially in young individuals who are relatively and absolutely in good health. Sprague and White[2] also comment that in young people high-grade heart block may not be serious prognostically, and Harris[3] in reporting a case of 28 years' duration stresses the fact that total block is compatible with normal life and that the prognosis depends on the degree of myocardial involvement. In a recent communication by Ellis and Weiss[4] a study of the effect of heart block on the circulation as a whole was reported and an explanation given of the mechanism by which the organism adjusts itself to the altered circulatory conditions. The purpose of the present investigation was to gain further information regarding the factors which govern the occurrence of symptoms and which determine the prognosis as to life from an analysis of a series of cases of complete heart block.

Incidence. The present series includes all of the cases, proven by electrocardiogram, admitted to the Boston City Hospital from 1920 to 1931. There are 40 of these; and during this period a total number of 7515 electrocardiograms were taken. The total number of cases is brought to 43 by the addition of 3 cases from the Children's Hospital, Boston. These 3 represent the only proven cases observed at that hospital during the past 10 years, although electrocardiographic tracings have been taken there only during the past year, a total of 151 tracings having been made. Thirty-five of the 43 patients have been followed to the present time or until death. Twenty-nine showed persistent complete block while under observation, in 3 the block was intermittent, and in the remaining 11 it was temporary.

The patients ranged in age from 9 weeks to 78 years (Table 1). In general, the cases can be divided into two main groups, those below and those above 40 years of age. Seventy per cent of the cases occurred in the latter division. When the deaths in these age groups are considered, the increased mortality in the older persons is strikingly evident. All of the 10 persons below 40 years of age who have been followed are living; only 5 of the 25 who were 40 years of age or older are still alive. This marked difference in death rate is chiefly explained by the change with advancing age in the etiologic causes of the heart block, as will be demonstrated below.

Thirty of the patients were male and 13 female, a ratio of somewhat over 2 to 1. This predominance of heart block in males has been noted before.[1,5,6]

TABLE 1.—AGE AND SEX DISTRIBUTION OF PATIENTS WITH COMPLETE HEART BLOCK AND MORTALITY IN VARIOUS AGE GROUPS.

Age, years.	No. of male patients.	No. of female patients.	Total patients.	No. of patients followed.	No. of followed patients living.	Followed patients living, per cent.
0 to 9	2	0	2	2	2	100
10 to 19	1	0	1	1	1	100
20 to 29	3	1	4	4	4	100
30 to 39	5	1	6	3	3	100
40 to 49	0	1	1	1	0	0
50 to 59	6	4	10	8	2	25
60 to 69	3	6	9	7	2	29
70 to 79	10	0	10	9	1	11
Total	30	13	43	35	15	43

Etiology (Table 2). The chief causes of total block are congenital defects, trauma, acute infections, intoxications as from digitalis, rheumatic fever, syphilis, arteriosclerosis and tumor. It is frequently impossible to determine with exactness clinically the etiology of complete heart block. This is especially true in young patients with no other evidence of cardiac disease. In a certain number of these individuals the heart block may be of congenital origin, in others it may have its inception during the course of some acute infection.

TABLE 2.—ETIOLOGICAL DISTRIBUTION OF PATIENTS WITH HEART BLOCK, WITH ITS RELATION TO AGE AND MORTALITY.

Etiology.	No. of patients.	Per cent of total patients.	No. of patients followed.	No. of followed patients living.	Per cent followed patients living.	Age limits of patients, years.	Average age of patients, years.
Permanent heart block:							
Congenital or unknown	9	31	7	7	100	<1–36	21
Diphtheria	1	3	1	1	100	27	27
Rheumatic fever	2	6	2	1	50	52–57	55
Arteriosclerosis	15	52	12	3	25	54–78	63
Arteriosclerosis and syphilis	1	3	0	..	...	54	54
Myxedema and syphilis	1	3	1	0	0	70	70
Total	29	..	23	12	52	<1–78	49
Intermittent or temporary heart block:							
Digitalis	8	57	7	2	29	21–73	58
Arteriosclerosis	4	28	4	0	0	49–76	62
Infection	2	14	1	1	100	29–53	41
Total	14	..	12	3	25	21–76	57

In the present series, of the 29 patients who showed a persistent block, there were 2 instances which were apparently of definite congenital origin, one in a child 9 weeks of age, and the other in a boy 9 years of age who had been known to have had a slow pulse rate since birth. Both had enlarged hearts with signs suggestive of congenital defects.* In 7 persons, all under 40 years of age, the etiology was undetermined, but the block was probably of congenital origin or followed some acute infection. Diphtheria was the probable cause in 1 person. This was the case of a young woman now 28 years of age in whom the sudden onset of a slow heart rate was observed during the course of a severe attack of diphtheria 24 years ago. This block has persisted to date, without giving rise to any disability or signs of cardiovascular disease. The rarity of persistent complete heart block with survival occurring during diphtheria has been previously noted.[7] In only 4 of all the cases here reported was any definite history of diphtheria obtainable. This is in contrast to the observations of Butler and Levine[8] who report that a history of diphtheria is more frequent in patients subsequently developing heart block than in a control series.

Two patients had a rheumatic cause. In 15 patients, 52 per cent of all of the cases of permanent heart block, arteriosclerotic changes were the probable cause of the block. Although syphilis is commonly considered one of the important etiologic causes of this condition, the blood Wassermann reaction was positive in only 2 of the 43 cases and both had an additional etiologic background, 1 of arteriosclerosis and the other of arteriosclerosis and myxedema, which very likely were primarily responsible for the lesion.

There were 3 patients, all with arteriosclerosis, with an intermittent complete block. Of the 11 cases of temporary auriculoventricular dissociation, 8 were apparently due primarily to digitalis. In 1 patient the only discernible cause was arteriosclerosis, and in the remaining 2 the temporary block occurred during the course of acute infections, 1 of acute rheumatic pancarditis and the other of septic sore throat.

Duration of Symptoms and Prognosis. The following analysis is confined to the 35 patients who were followed until the present time or death. Twenty-three of these showed a permanent block, and 12 had transitory *A–V* dissociation.

(*A*) *Permanent Heart Block.* The 7 patients with either a congenital or undetermined etiology for their heart block were all under 40 years of age and are all living. Four have no symptoms whatsoever in spite of leading active lives and 3 have only mild symptoms. In 2 of these persons there is good evidence that the block has existed for at least 9 years, and in a third it is known to have been present for over 7 years.

* These 2 cases and 1 other will be reported in detail from the Children's Hospital.

The patient with block of diphtheritic origin of 24 years' duration is living and without symptoms.

Of the 2 patients in whom rheumatic infection was the etiologic agent, 1 had been a chronic cardiac invalid for years and died 30 months after the discovery of the block. The other is living but has experienced repeated severe attacks of congestive heart failure.

Three of the 12 individuals with arteriosclerotic heart block are living, and all of them have cardiac symptoms of slight to moderate extent. In the remaining 9 the duration of life after the discovery of the heart block was as follows: 1 lived five years with frequent Adams-Stokes attacks; 1 lived 3 years with increasing cardiac symptoms; 4 lived 2 to five months; and the remaining 3 died in less than 2 weeks.

The patient with heart block probably due to myxedema, arteriosclerosis and syphilis died suddenly of undetermined cause after having been observed for 5 years, during which time he experienced continually moderate symptoms of weakness and dyspnea.

One of the 12 living patients, a woman 68 years of age, has had infrequent Adams-Stokes attacks for the past 7 years. Seven of the 11 individuals who died were subject to such attacks of varying degrees of frequency and severity.

The lowest pulse rate in the patients with permanent block was 23, the highest 65 per minute. The majority fell between 30 and 50. No relationship was found between the pulse rate and the symptoms or mortality.

(*B*) *Temporary Heart Block.* Twelve patients with temporary or intermittent complete heart block have been followed. In 7 of these the etiologic agent appeared to be primarily digitalis intoxication, and all developed a normal rhythm within a few days after the digitalis was omitted. Two are living 2 and 5 years respectively after the occurrence of the heart block, 1 died of carcinoma about a year after the block, and 4 died of heart failure in from a few weeks to 18 months following the block. Two of the latter had complicating factors in the causation of the block; one, coronary thrombosis and the other, subacute bacterial endocarditis.

The patient who developed a complete block of short duration during the course of septic sore throat is now living and well 5 years later. The 4 persons with an arteriosclerotic background all died after pronounced cardiac symptoms had existed for 2, 3, 6 and 7 months respectively. Three of these individuals had varying degrees of block during the greater part of the time they had symptoms, although complete block existed in each for relatively short periods.

Three of the 4 persons dying with arteriosclerotic heart block had repeated Adams-Stokes seizures. None of the other patients subsequently dying developed such attacks. Of the living patients, the one whose block occurred during septic sore throat had several

attacks while the block persisted but none since. None of the other living patients showed this symptom.

The ventricular rates in the group showing temporary heart block varied from 33 to 100 per minute, all but 3 falling between 33 and 50. No correlation was found between the cardiac rate and the etiology, course or outcome.

Cardiac Enlargement. Only 7 of the 43 cases analyzed showed no cardiac enlargement. In these 7 patients the blood pressures were normal. Six of the 35 cases followed showed no enlargement; 5 of these are still living and have a diverse etiology. It is thus apparent that although cardiac enlargement in heart block may exist in persons in a relatively good state of health, it is unusual for the hearts of patients with this condition to be of normal size in the presence of marked myocardial damage, particularly if the blood pressure is elevated.

Electrocardiographic Findings. Five of the 43 patients had auricular fibrillation with complete block. An analysis of the electrocardiographic tracings in the 35 patients who were followed is given in Table 3. The greater frequency of abnormalities usually

TABLE 3.—ELECTROCARDIOGRAPHIC ABNORMALITIES ACCOMPANYING COMPLETE HEART BLOCK.

	Type of heart block.				
	Permanent.		Temporary.		
	Alive.	Dead.	Alive.	Dead.	Total.
Total patients followed	12	11	3	9	35
No abnormality*	7	3	2	4	16
Auricular fibrillation	1	2	0	1	4
Intraventricular block	1	2	0	2	5
Bundle-branch block	0	2	1	0	3
Inverted or diphasic T_1 or T_2	3	2	0	2	7
Patients with no abnormality, per cent*	58	27	67	44	46

* Not including the heart block or axis deviation.

considered indicative of cardiac damage among the patients that died is evident. In many instances the electrocardiograms were taken months and even years before the death of the patients so that the abnormalities encountered do not necessarily represent terminal electrocardiographic changes.

Six of the 43 patients showed an irregularity in the spacing of the *P–P* intervals commented upon by Wilson and Robinson.[9] When a ventricular complex fell between the *P* waves the *P–P* interval was distinctly shorter than when no ventricular complex intervened. Two of these persons are known to be living and symptomless with heart block of congenital and diphtheritic etiology respectively, 1 had temporary block of arteriosclerotic origin and is dead and 3 have not been followed. The etiology in 1 of these 3 cases was arteriosclerosis and in 2 undetermined.

Twenty-two patients showed left axis deviation, 1 right axis

deviation, 4 bundle-branch block, and 16 normal axis. No correlation was found between the axis and the etiology, functional condition, or mortality.

Arterial Blood Pressure. It is commonly held that in complete heart block there is characteristically an increased systolic and a normal diastolic pressure, resulting in a distinct and often very marked widening of the pulse pressure. So far as the diastolic pressure is concerned the findings in this series support such a belief. In only 3 of the 43 cases was the diastolic pressure 100 mm. of mercury or over. In the great majority of patients it fell between

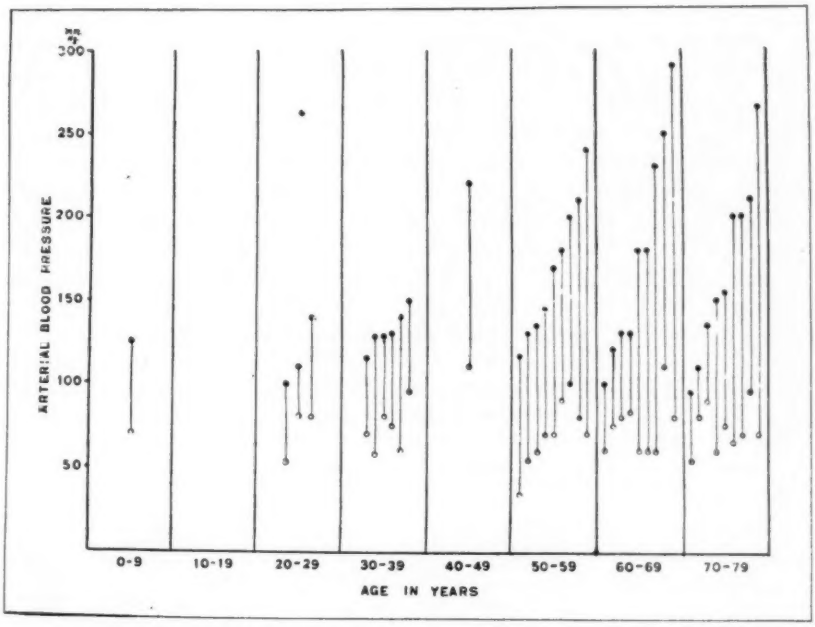

CHART I.—Arterial blood pressure in various age groups of patients with complete heart block. Solid circles represent the systolic, and hollow circles the diastolic pressures.

60 and 80 mm. of mercury. A markedly increased pulse pressure, *i.e.*, a systolic hypertension, was found to occur, however, only in the older age groups (Table 4, Chart I). This corroborates results previously reported by Ellis and Weiss[4] which indicate that in complete heart block a definitely widened pulse pressure occurs usually only when the peripheral vascular system is sclerosed. The converse finding, that of low systolic and relatively low pulse pressures in patients with arteriosclerosis, observed in a few cases of the present series, is probably caused, in part at least, by failing cardiac function.

TABLE 4.—ARTERIAL BLOOD PRESSURES AND PULSE PRESSURES IN VARIOUS AGE GROUPS.

Age.	No. of patients.	Average arterial blood pressure.		Range of pulse pressure, mm. Hg.	Average pulse pressure, mm. Hg.
		Systolic, mm. Hg.	Diastolic, mm. Hg.		
0 to 9	2	125	70	55	55
10 to 19	1				
20 to 29	4	116	71	30–60	45
30 to 39	6	131	73	45–80	60
40 to 49	1	220	110	110	110
50 to 59	10	163	69	75–170	101
60 to 69	9	190	74	50–210	107
70 to 79	10	169	73	40–195	95

The effect of age and the state of the peripheral vascular system on the pulse pressure is illustrated more strikingly if groups are compared in which the possible influence of myocardial failure on the blood pressure has been eliminated. In Table 5 this is done. The first group is of young persons with no evident arteriosclerosis or myocardial damage other than the heart block. The second group comprises persons 50 years of age or older with varying degrees of arteriosclerosis but with very slight or no cardiac symptoms. The difference in pulse pressures is immediately apparent. None of the young persons had pulse pressures in excess of 60; only 2 of the old patients showed pulse pressures below 70.

TABLE 5.—COMPARISON OF ARTERIAL BLOOD PRESSURES IN PATIENTS WITH AND WITHOUT ARTERIOSCLEROSIS.

Patients with no evidence of myocardial damage or arteriosclerosis.					Patients with evidence of arteriosclerosis but having no or slight symptoms.				
Patient.	Age.	Arterial blood pressure, mm. Hg.		Pulse pressure. mm. Hg.	Patient.	Age.	Arterial blood pressure, mm. Hg.		Pulse pressure. mm. Hg.
		Systolic.	Diastolic.				Systolic.	Diastolic.	
1	33	128	80	48	8	60	132	80	52
2	33	115	70	45	9	68	290	80	210
3	29	110	80	30	10	70	150	60	90
4	21	100	55	45	11	70	135	88	47
5	36	150	95	55	12	50	200	100	100
6	9	125	70	55	13	65	250	110	140
7	28	140	80	60	14	53	116	34	82
					15	58	145	70	75
					16	78	265	70	215
					17	58	240	70	170

If the blood pressures are analyzed according to etiology, the only correlation is that the causes which tend to affect the older age groups are accompanied by higher pulse pressures.

No correlation was found between the pulse rate and blood pressures.

In the instances in which blood pressures were recorded in persons both during complete heart block and when normal rhythm had been restored there was no constant tendency for the systolic or diastolic pressures to change in any given direction.

Discussion. The present series is too small to permit of significant statistical analysis. Certain definite facts appear, however, and from them conclusions may be drawn. Complete heart block *per se* does not necessarily jeopardize the health or life of the individual having it. This is particularly evident from a consideration of 4 of the relatively young persons in this series in 2 of whom the block is known to have existed for 24 and 7 years respectively, and in the other 2 to have been present almost certainly for 9 years, without objective or subjective evidence of cardiac deterioration or failure.

Dr. Paul D. White has kindly given me permission to mention here 2 of his cases of complete heart block. These are both in women; one is aged 41 years and the other is about 35 years old. They have been known to have had persistent heart block for at least 14 and 15 years respectively. Both have been followed clinically and checked by electrocardiogram during this time. In neither was the etiology determined. Both are quite well and lead active lives, 1 being an ardent and excellent golfer. Instances have been reported in the literature of total heart block existing in persons in good health for many years, notably the case reported by Harris[3] of 28 years' duration, and that by Willius[6] lasting 15 years.

Heart block should not, therefore, be considered a disease entity either from the etiologic or prognostic viewpoint. It should rather be considered merely as a sign of cardiac abnormality which is usually indicative of severe cardiac damage. The regulation of the life and the prognosis given an individual depend on a consideration of other aspects of his condition. These are: (1) The underlying etiology. When the block is due to arteriosclerosis it is usually indicative of widespread cardiac damage, whereas if the etiology is of congenital or undeterminable origin, the block is more likely to be caused by a localized lesion or defect in the conducting system and the myocardium may be unimpaired; (2) with increasing age the prognosis becomes worse, probably due to a shift in the predominating etiologic causes with advancing age; (3) Adams-Stokes attacks usually are of grave import, indicating as they do periodic circulatory insufficiency, ordinarily due to a breakdown in the conducting and exciting mechanism of the heart; (4) any of the electrocardiographic changes usually considered an indication of cardiac damage are evidence of poor cardiac function; (5) a normally-sized heart in a patient with total block indicates an adequately functioning myocardium and carries a better prognosis. From no one of these factors alone should a prognostic conclusion be drawn,

but from an evaluation of all of these aspects a decision can be reached as to the significance of the lesion and the probable future progress of the condition.

In the previous study of heart block reported by Ellis and Weiss a picture of the functioning and adjustments of the circulation as a whole was presented. The present clinical study supports the previous findings, in particular regarding the arterial blood pressure in heart block. The systolic hypertension and increased pulse pressure frequently observed in complete heart block have been considered an index of the increased ventricular discharge by most observers. While undoubtedly there is an increased cardiac stroke output in this condition, this usually occasions a greatly increased pulse pressure only when the peripheral arterial system is so rigid, through sclerotic changes, that a high initial systolic pressure becomes essential to maintain the forward movement of the blood during the prolonged diastolic pauses. In young persons, without arteriosclerosis, the elastic vessels can stretch to accommodate the increased mass of blood projected into them with each beat, and by contracting aid in its forward propulsion without the necessity for a raised systolic pressure. Such young individuals are spared, therefore, the added strain which hypertension in itself imposes on the heart and circulation. All of the patients of this series who were relatively young and without evidence of peripheral sclerosis had arterial blood pressures which did not differ strikingly from the normal.

Summary. 1. An analysis is presented of 43 cases of complete auriculoventricular block in patients ranging in age from 9 weeks to 78 years. Seventy per cent of the patients were over 40 years of age and the same percentage were males. In 29 cases the block was permanent, while in the remainder it was intermittent or temporary.

2. Fifty-two per cent of the cases of permanent block were due to arteriosclerosis, 31 per cent were of undetermined origin, but in most of these instances were probably either congenital or dependent upon an acute infection. Diphtheria, syphilis and rheumatic infection were responsible for a small number of cases. Digitalis was the chief etiologic agent producing transitory block, although arteriosclerosis and infections caused a lesser proportion.

3. Complete heart block *per se* may exist for very prolonged periods of time without damaging the health of the patient. Four cases are recorded in which the block is known to have existed for 24, 15, 14 and 7 years respectively, and 2 more in which it has almost certainly lasted 9 years. The chief factors governing the prognosis appear to be etiology, age, Adams-Stokes seizures, electrocardiographic abnormalities, and cardiac size.

4. A discussion of the significance of arterial blood pressure findings is presented. Young persons with complete heart block

may have essentially normal blood pressures. A systolic arterial hypertension and wide pulse pressure usually occur in heart block in persons giving evidence of peripheral arteriosclerosis.

NOTE.—It is a pleasure to acknowledge my appreciation to Dr. Kenneth D. Blackfan of the Children's Hospital, Boston, for permission to report the cases from that hospital, and to Miss Mildred Adell for assistance in following the patients.

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THE COLONIC ADMINISTRATION OF OXYGEN IN EXPERIMENTAL ANOXEMIA.

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THE 4 experiments to be reported in this paper were undertaken to determine whether within a given period of time a sufficient amount of oxygen would be absorbed from the colon of a dog to relieve or abolish a degree of experimental anoxemia comparable to that which is sometimes seen clinically in human disease. Such a study seemed capable of yielding knowledge of practical importance when we recalled the following known facts:

1. The value of oxygen as a therapeutic measure. At the present time its use is widespread and those who have had most experience

with it are uniformly agreed as to its value as a therapeutic agent. Its ability to raise the oxygen content and per cent oxygen saturation of the arterial blood in most cases of acute pneumonia with anoxemia was clearly demonstrated by a study of the blood gases in 137 cases of pneumonia at the Hospital of the Rockefeller Institute before and after exposure to a 40 per cent oxygen concentration in a specially made chamber (Binger[1]).

2. Its inability, when given by inhalation, to abolish or relieve anoxemia in the occasional case of pneumonia with extensive pulmonary involvement and "wet" lungs.

3. The relative scarcity and limited accommodations of oxygen chambers, even though it is uniformly conceded that the chamber is the most efficient and most convenient means of giving oxygen and by far the most pleasant for the patient.

4. The inaccessibility of oxygen tents which are recommended as the second best means of giving oxygen; and the inconvenience and noise which are associated with their use.

5. The discomfort and limited effectiveness of the administration of oxygen by means of nasal catheters or face masks.

6. The fact that the absorption of oxygen from the gastrointestinal tract has been demonstrated experimentally.

When these facts were considered it occurred to us that the effective and harmless administration of oxygen by some route other than the lungs would not only be of interest but under certain clinical conditions was actually indicated. We knew that this idea had occurred to others, but found no reports in the literature, either experimental or clinical, of the absorption of oxygen through the colon at a sufficient rate to raise the per cent oxygen saturation of the arterial blood in anoxemia.

Kato[2] studied the changes in various gases which he introduced into isolated sections of the small intestine of anesthetized rabbits and found that carbon dioxid disappeared rapidly, oxygen slowly and hydrogen and nitrogen not at all. He noted further that small amounts of carbon dioxid and nitrogen appeared in the intestinal lumen after the injection of hydrogen and nitrogen and caused an increase in the original volume. Schoen[3] made similar studies on dogs, including the large intestine, and in general noted the same results. These studies by Kato and Schoen and more recent studies by McIver, Redfield and Benedict[4] and others indicate that there is an interchange of gases between the lumen of the gastrointestinal tract and the circulating blood, which resembles the gaseous interchange in the lungs and which, like it, is governed by the physical laws of diffusion.

The slow absorption of oxygen was not encouraging for the study which we had planned. Nevertheless, it must be borne in mind that the observations alluded to were made on animals whose blood, presumably, was normally saturated with oxygen. Assuming an

adequate supply of oxygen through the colon, the tendency for it to be absorbed would be greater when the oxygen tension of the blood is low and there is consequently a greater difference between the partial pressure of the gas within and without the lumen of the gut. Such were the conditions in our experiments. Our results, however, were disappointing in that they were negative and whatever importance can be attached to them would seem to lie in the field of academic rather than of practical interest.

Method. Dogs were used. Each animal received 2 colonic irrigations with warm suds, 1 on the day preceding and the other on the morning of the experiment. Several hours after the second irrigation the animal was anesthetized by the intravenous injection of barbital sodium (0.3 gram

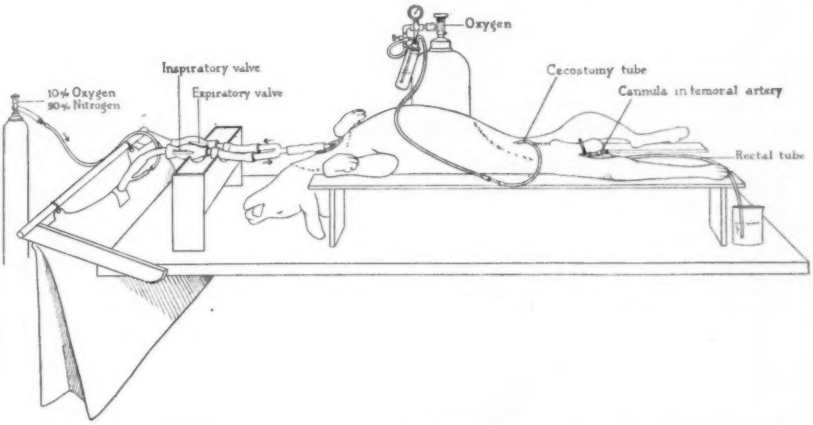

FIG. 1.—Diagrammatic view of the apparatus which was used in Experiments 3 and 4. In Experiments 1 and 2 oxygen was administered through the rectal tube and the cecostomy was not necessary. Otherwise the preparation used in these two experiments was identical with the one shown in the diagram.

per kg. body weight). The trachea was isolated through a midline incision, opened horizontally, and a glass cannula tied snugly in position. A second cannula was then inserted into one femoral artery for the withdrawal of blood samples. At the end of a control period, during which the animal breathed room air, the first blood samples were taken. Immediately after this the tracheal cannula was connected through a system of inspiratory and expiratory valves with a Douglas bag containing a gas mixture of 90 per cent nitrogen and 10 per cent oxygen (Fig. 1). By causing the animal to inspire from the bag and expire into room air, the oxygen percentage of the inspired air was maintained at a constant low level. In this way the oxygen tension of the alveolar air was reduced to such a degree that anoxemia regularly resulted. After the animal had breathed this oxygen-poor mixture for a given period of time (varying from 12 to 19 minutes) second blood samples were withdrawn in order to determine the degree of anoxemia which resulted. The administration of oxygen was then begun. In the first experiment (No. 1) 3000 cc. of oxygen were introduced through a rectal tube during a period of 15 minutes. In the second (No. 2) 5500 cc. were given during a period of 61 minutes. In the third and fourth experiments

the oxygen was introduced at a given rate through a small rubber catheter which previously had been fixed in the cecum and allowed to pass through the colon and out through a rectal catheter, the end of which was immersed in water. In these two experiments oxygen was administered for periods of 20 and 30 minutes respectively. The third blood sample was then taken, the administration of oxygen discontinued and the animal again allowed to breathe room air. From 6 to 19 minutes later a final sample of blood was withdrawn. At frequent intervals during the progress of each experiment the pulse and respiratory rates were counted with the aid of a stopwatch.

The oxygen content of the blood samples was estimated by the manometric method of Van Slyke and Neill[5] and the results expressed in volumes per cent. The oxygen capacity of each sample was estimated after rotating the blood for 5 minutes in a flask in which it was exposed to room air. The percentage saturation of the arterial blood with oxygen was calculated by dividing oxygen content by oxygen capacity. The blood samples were transferred to oxalated tubes beneath oil and kept in the ice box until analyzed. Analyses were done in duplicate and results which did not agree within five-tenths of 1 per cent were discarded.

The animals were killed while still under the influence of the anesthetic by injecting 10 cc. of a saturated solution of magnesium sulphate into the femoral artery and an autopsy was performed immediately. The position of the rectal catheter was noted and sections of the colon were taken for microscopic study.

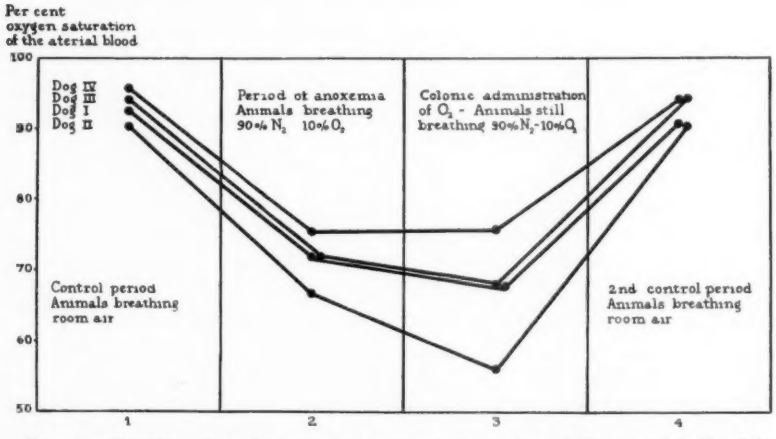

FIG. 2.—Showing that the per cent oxygen saturation of the arterial blood in experimental anoxemia was not increased by the colonic administration of oxygen. The duration of each period in minutes is included in Table 1.

Results. The inhalation of a gas mixture containing 90 per cent nitrogen and 10 per cent oxygen was followed in all of the experiments by a pronounced decrease in the oxygen saturation of the arterial blood. During the control period with the animals breathing room air the oxygen saturation of the arterial blood varied between 90.3 and 95.9 per cent and averaged 93.9 per cent. During the inhalation of the oxygen-poor mixture the per cent oxygen saturation of the arterial blood varied between 66.9 and 75.3 and averaged 71.7. The administration of oxygen, either by rectal tube

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA.

Experiment No. and sex.	Date.	Weight, kg.	Time, minutes.	Conditions.	Arterial blood.			Respiratory rate per minute.	Pulse rate per minute.
					Oxygen content per cent by volume.	Oxygen capacity per cent by volume.	Oxygen saturation, per cent.		
1. Female	January 14, 1931	12.7	1:40	Breathing room air	12.7	13.7	92.7	60	190
			1:50	Breathing 90% N_2, 10% O_2					
			2:01	.....	10.2	14.1	72.3	43	245
			2:02	Administration of oxygen through rectum begun					
			2:19	.....	9.6	14.1	68.1	64	244
			2:21	Breathing room air					
			2:27	.....	12.5	13.8	90.6	54	246
2. Male	January 21, 1931	23.0	1:37	Breathing room air	15.8	17.5	90.3	14	134
			1:50	Breathing 90% N_2, 10% O_2					
			2:03	.....	11.9	17.8	66.9	19	131
			2:05	Administration of oxygen through rectum begun					
			3:10	.....	10.5	18.7	56.1	18	112
			3:11	Breathing room air					
			3:20	.....	15.7	17.4	90.2		
3. Male	January 28, 1931	7.6	3:50	Breathing room air	15.2	16.1	94.4	10	105
			4:04	Breathing 90% N_2, 10% O_2					
			4:21	.....	12.3	17.0	72.3	16	102
			4:22	Administration of oxygen through cecum begun					
			4:45	.....	12.2	17.9	68.2	18	104
			4:47	Breathing room air					
			5:00	.....	17.1	18.1	94.5	5	102
4. Male	February 4, 1931	10.4	2:40	Breathing room air	18.6	19.4	95.9	40	140
			2:49	Breathing 90% N_2, 10% O_2					
			3:05	.....	15.6	20.7	75.3	30	150
			3:08	Administration of oxygen through cecum begun					
			3:28	.....	15.9	21.0	75.7	52	150
			3:31	Breathing room air					
			3:50	.....	20.1	21.3	94.4	46	148

or through a cecal catheter, was not accompanied by any significant change in 3 experiments (Nos. 1, 3 and 4). In experiment 2, after prolonged inhalation of the 10 per cent oxygen mixture, the oxygen saturation of the arterial blood fell from 66.9 per cent to 56.1 per cent while oxygen was being given by rectum. It is possible that this was due to the damaging effect of long continued oxygen want on the circulatory system. During the colonic administration of oxygen the saturation of the arterial blood varied between 56.1 and 75.7 per cent, averaging 67 per cent. When the animals were allowed to respire room air again, the oxygen saturation of the arterial blood quickly returned to the control levels. The experimental data are summarized in Table 1 and shown graphically in Fig. 2.

At autopsy it was noted in all of the experiments that the end of the rectal catheter lay in the upper part of the descending colon. There was no gross evidence of trauma. Microscopic examination of the excised sections of the colon did not reveal any significant variations from the normal. Distention of the small intestine was not found in any instance and we were never able to force oxygen through the ileocecal valve after death by using a degree of pressure comparable to that which was employed in the experiments.

Discussion. In accordance with the physical laws of gaseous diffusion, if a gas is to be absorbed from the intestinal tract, it is necessary that the tension of the gas within the lumen of the gut always exceed the tension of the gas in the blood circulating in its wall. If this condition is satisfied the rate of absorption will depend largely on the magnitude of the difference between the two tensions, the diffusibility of the gas in question and the relative permeability of the interposed tissue. The amount of gas which will be aborbed in a given time will be determined by the rate of diffusion and the total area of the exposed surface. In our experiments these conditions have to be considered only in relation to the colon, because the oxygen which we introduced never went past the ileocecal valve to enter the small intestine.

In view of the degree of anoxemia which was produced and the rate at which pure oxygen was administered it is reasonable to assume that a wide difference between the oxygen tension within and without the gut was continuously maintained in our experiments. Therefore, we must look to the other conditions stated above for an explanation of the failure of the animal to absorb oxygen in sufficient amounts and at a sufficient rate to increase the per cent oxygen saturation of the arterial blood. All of these conditions were unfavorable. The diffusion rate of oxygen is low; the permeability of the colonic mucous membrane in all probability is small as compared to that of the thin epithelial lining of the alveolar spaces; the total surface area for absorption is markedly less than that in the lungs and, finally, and perhaps most important of all,

the amount of blood circulating through the colon is a relatively small fraction of the total bloodflow. Doubtless all of these factors, in varying degrees of importance, were responsible for the negative results which were obtained.

Summary. 1. A pronounced drop in the per cent oxygen saturation of the arterial blood of anesthetized dogs was regularly produced by causing the animals to breathe a gas mixture containing 90 per cent nitrogen and 10 per cent oxygen.

2. The colonic administration of oxygen (either by rectum or through a cecostomy tube) did not raise the arterial saturation.

3. Gross and histologic examinations of the colon showed no evidence of injury.

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STUDIES IN REVIVIFICATION.

I. ORGANIZATION OF RESUSCITATION MEASURES.

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THE purpose of the experiments reported in this paper was the establishment of an orderly routine for the resuscitation of animals in which sudden death had been brought about by volatile anesthetics, asphyxia, hemorrhage or electrocution. Since clinical application was the goal of the research, a definite, rigid procedure was developed; a procedure which in our hands resuscitated 82 per cent of our 52 cats, and 52 per cent of our 29 dogs. Early experience demonstrated the necessity of adhering closely to a definite method.

Any variation in the sequence of our procedures made resuscitation more difficult.

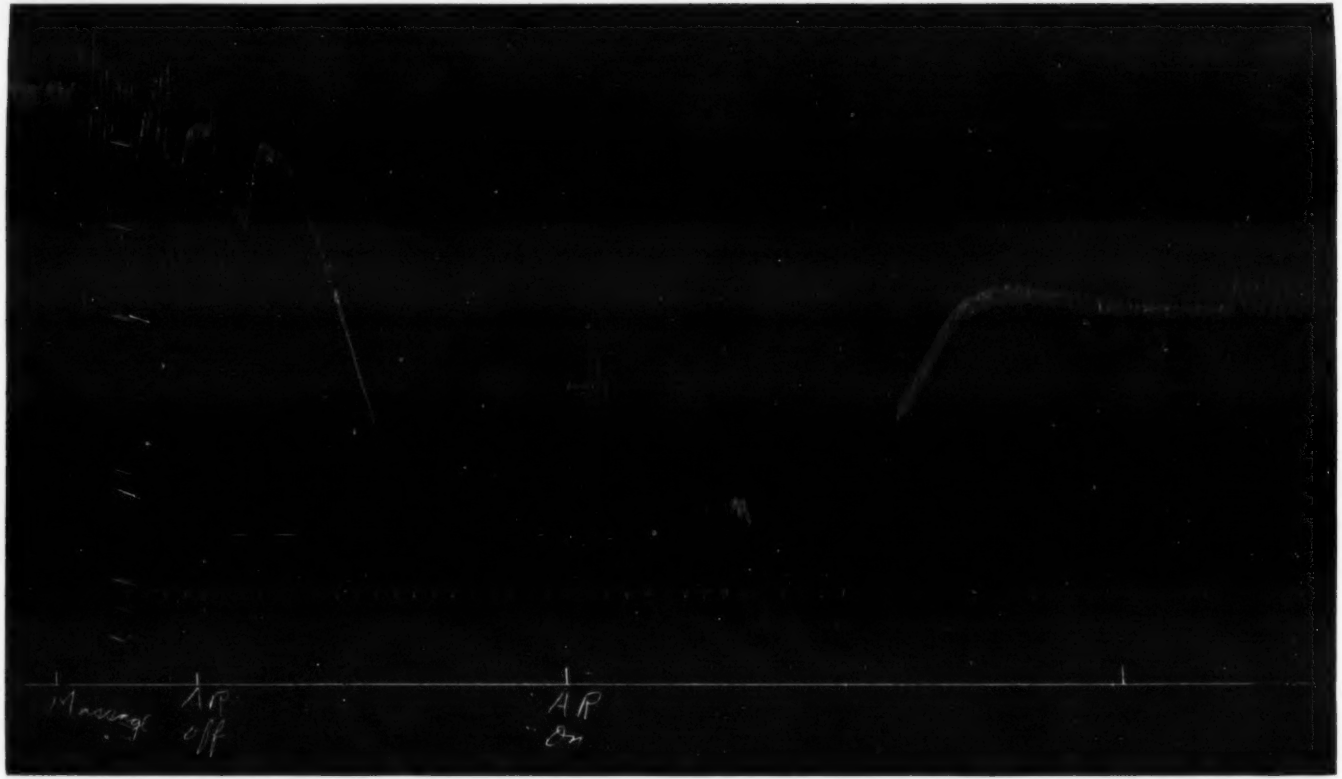
Regardless of the cause of death, the 2 principal conditions to be overcome in resuscitation are respiratory failure and circulatory collapse. Primary circulatory collapse may be due either to cardiac arrest or to central vasomotor paralysis. Respiratory depression may be due to the direct action of a toxic substance on the center, or may be secondary to circulatory collapse. In primary respiratory failure, the heart continues to function for a variable length of time, but eventually dies of asphyxia. Respiratory depression leads to accumulation of carbon dioxid and exhaustion of oxygen. The primary effect of the excess of carbon dioxid in the blood stream is a stimulation of the respiratory center, with a deepening and acceleration of breathing. Excessive stimulation in the presence of oxygen-lack soon leads to paralysis of the respiratory center. The vasomotor center is also very susceptible to asphyxia, but of all the vital centers, it seems to be the most resistant to permanent injury.

In 73 experiments in which an overdose of ether was administered, the respiratory center failed before the heart in 70 (96 per cent), while in 3 (4 per cent) circulatory collapse and respiratory failure occurred simultaneously. When concentrated doses of chloroform were employed, cardiac arrest preceded the respiratory paralysis in every instance. A minimum lethal electric shock invariably produced ventricular fibrillation, in cats, dogs and guinea pigs; respiratory movements continued for varying periods after the blood pressure had fallen to zero.

Despite the fact that the circulatory system may be depressed by one agent and the respiratory mechanism by an entirely different cause, the two systems are normally absolutely dependent one on the other; depression of one invariably affects the other; paralysis of one always results in the ultimate paralysis of the other. It is evident, therefore, that simultaneous treatment for both respiratory and circulatory failure becomes imperative in every instance; the essential problem is to supply oxygen to, and remove carbon dioxid from the tissues.

Experimental Results. Our findings are best described under three headings. In these experiments dogs and cats were given lethal doses of chloroform, ether or electric shock. In some cases, the same animal was killed and resuscitated repeatedly; 1 cat was resuscitated 9 and another 12 times.

Series 1. Fifty-three experiments were performed in which resuscitative measures consisted of artificial respiration alone. This measure succeeded in reëstablishing an efficient circulation and respiration in some animals, but failed in others. An analysis of our data showed that artificial respiration was successful in those animals which (because of the absence of pulse, cardiac sounds and



X (see legend)

FIG. 1.—Blood pressure tracing (Hg. manometer) cat. Asphyxial death. Blood pressure falling from 130 mm. to zero; animal pulseless; no cardiac sounds or respiratory movements. Electrocardiogram showed weak auricular and ventricular contractions. Circulation and respiration restored by artificial respiration and manual compression of chest. Time, five seconds. A. R. off and A. R. on = artificial respiration stopped and begun. X = spontaneous respiratory gasp.

respiration) we considered dead (Fig. 1); the electrocardiogram indicated, however, that the heart was beating. Artificial respiration alone always failed to resuscitate the animal, when the respiration was at a proven standstill. Since oxygen is a primary necessity of life, our first consideration was the means of supplying oxygen to the organism; so some form of artificial respiration must be instituted as soon after cardiorespiratory failure as possible. Three different methods of artificial respiration were successively tried. A metal cannula was tied into the trachea, and the depth and rate of respiration were regulated by a Becker interrupter. To obviate tracheotomy, a method of manual compression of the thorax was developed and was found effective. Finally, in order to prevent exhaustion of the operators, insufflation through a rubber catheter introduced into the trachea was adopted. The air blown into the animal was warmed and moistened.

Since at the time of a serious clinical accident, apparatus for carrying out artificial respiration is not always available, the efficacy of various types of manual compression of the thorax was tested. The best results were obtained by using the Schaffer method, modified by placing the animal on its back. Compression of the thorax must be effective in maintaining pulmonary ventilation without, at the same time, doing harm to vital organs. With this type of artificial respiration, too violent manipulation may cause severe injury to the lungs and liver.

The following protocol illustrates the typical results obtained by various measures after complete failure of respiration and circulation.

Experiment 1.—(Fig. 2.) May 26, 1930. Cat, female, 2.3 kg. Carotid artery, femoral vein and trachea cannulized. Blood pressure, 115. mm. Hg.

0:07. Inhalation of excessive concentration of warmed ether.

0:08. Respiration shallow and slow. Blood pressure temporarily fell, then rose above normal. (Asphyxial.)

0:09. Breathing failed; blood pressure dropped to zero; heart feebly beating.

0:10. Heart stopped.

0:11. Mechanical artificial respiration instituted; tight binder applied to abdomen and lower chest; animal placed in extreme shock position.

0:12. Extrathoracic manual compression begun and continued for 1 minute without reinstating natural breathing or arousing the heart.

0:13. Epinephrin (1 to 1000, 0.1 cc. per kg.) injected into femoral vein; no cardiac response.

0:13. Epinephrin driven toward the heart by intravenous injection of saline solution (3 cc.) and by extrathoracic and abdominal massage. The heart immediately began to beat. Blood pressure rose gradually.

0:14. Artificial respiration interrupted at intervals to observe the recurrence of spontaneous breathing. Blood pressure continued to rise.

0:16. First spontaneous respiratory gasp.

0:17. Artificial respiration stopped.

0:18. Regular spontaneous breathing. Blood pressure remained at 150 mm. This was followed by the reappearance of the knee-jerk, voluntary movements and consciousness.

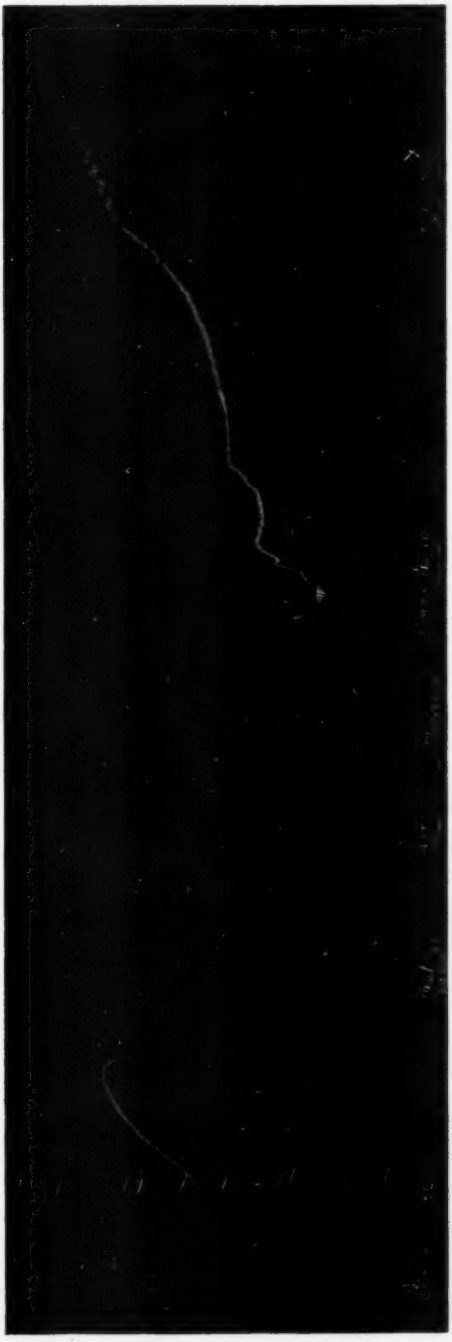


FIG. 2.—Blood pressure tracing of a cat. Ether death. Failure of artificial respiration and extrathoracic cardiac massage to restore the circulation. Successful restoration of circulation and respiration by combination of artificial respiration, extrathoracic cardiac massage and intravenous administration of epinephrin. Blood pressure zero 14 mm. above time marker. Time, five seconds.

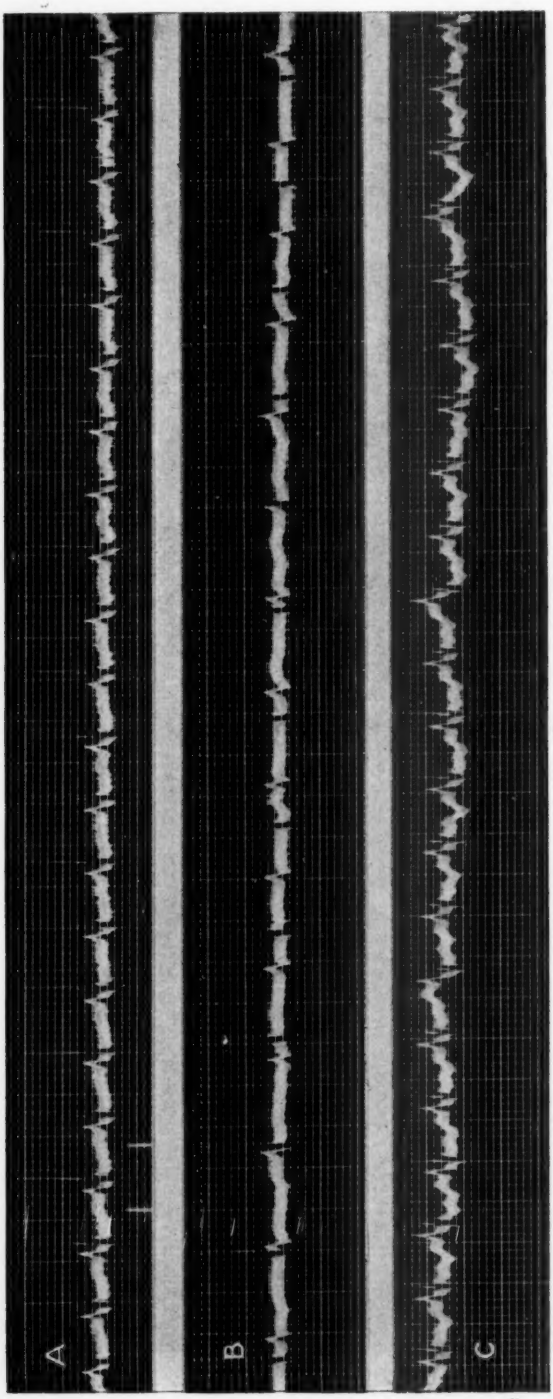


FIG. 3.—Electrocardiograms of cat. *A*, Light ether anesthesia—normal rhythm; *B*, "death" period, when blood pressure was 0 mm. and respiration ceased—complete auriculoventricular dissociation; *C*, recovery, with return of normal blood pressure and reinstatement of spontaneous respiration. N. B.—The R deflections, though faint, are definitely visible in the originals.

In this experiment, in which both respiration and circulation were at a standstill, artificial respiration alone was unsuccessful in reinstating the circulation. However, when the artificial respiration was combined with the administration of epinephrin and an orderly sequence of supportive measures, a complete revivification followed.

Since a feeble cardiac contraction is not generally perceptible by ordinary clinical methods of palpation and auscultation, the heart's action must be observed by direct inspection of the exposed organ or electrocardiographically. Inspection and the electrocardiogram show that the heart may continue to beat coördinately for several minutes after respiration ceases, blood pressure has dropped to zero, and the animal is pulseless. (Fig. 3.) The next phase of the heart's action may be a ventricular standstill, the auricle continuing to beat in orderly fashion until eventually the atrium stops in diastole. Utilizing the electrocardiographic means of determining the condition of the heart, we are able to show that artificial respiration alone is not sufficient to restore to activity a heart all of whose chambers are completely stopped. However, in the presence of any detectable cardiac acitivity, artificial respiration alone usually restores a useful circulation. Many of the reported successful resuscitations may very well have been of this type.

SERIES II consisted of 44 experiments (25 cats, 19 dogs) in which an attempt was made to standardize a method of inaugurating an artificial circulation which would delay the onset of asphyxia of the central nervous system. A total anemia of the central nervous system rapidly produces irreparable pathologic changes.[1] In resuscitation, therefore, the maintenance of the vitality of the central nervous system through the immediate reinstatement of a circulation becomes of primary importance. Often the heart continues to beat after respiration has stopped and blood pressure has fallen to zero. These slow, weak beats maintain a feeble circulation which postpones asphyxia, and prevents the threatened anemia of the central nervous system.[2]

Wolff and Lennox[2] have shown experimentally that cerebral anemia and asphyxia cause vasodilatation of the pial vessels. The first step for increasing the blood supply to the central nervous system is placing the animal in extreme shock position. This change of position favors drainage of the splanchnic area, and immediately encourages a maximal passive blood supply to the cerebral vessels. As an adjuvant to the shock position, tight binding of the abdomen and lower chest decreases the splanchnic blood bed, and assists further in driving blood to the anemic brain. There is a definite technique in applying the binder; pressure is made on the lower abdomen, forcing the viscera against the diaphragm; the binder is then pulled taut across the abdomen and lower chest, and secured with artery clamps from below upward. Artificial respiration in the

presence of the increased intraäbdominal and intrathoracic pressure causes effective massage of the heart by the lungs, thus forcing the blood out of the ventricles into the great vessels.

Direct cardiac massage maintains a fairly satisfactory circulation, and helps to delay asphyxia. Since this treatment is impractical clinically, another method of promoting circulation was employed, *viz.*, manual compression of the thorax. With each compression, the heart is emptied, and with each release of pressure the heart refills. Thus the artificial circulation already established by artificial respiration is enormously augmented. Our tracings show that this indirect massage of the heart is as effective in raising blood

FIG. 4.—A comparison of the effectiveness of maintaining a circulation by indirect cardiac massage (compression of the thorax), and direct massage of the heart.

pressure as is direct massage. (Fig. 4.) This propulsion of blood has been observed in the arteries, veins, and capillaries of the mesentery and the cerebrum of our experimental animals. The circulation thus artificially produced by shock position, abdominal binder, artificial respiration and indirect cardiac massage was sufficient to keep alive the respiratory and vasomotor centers, in several cases, for almost an hour, even though the heart remained absolutely quiescent.

Experiment 2. Cat, male, 3.3 kg. Ether anesthesia. June 18, 1930. Carotid artery, femoral vein and trachea cannulized. Blood pressure, 115 to 125 mm. Hg.

0:03. Electrocardiogram 1. (Normal.)

0:05. Electric shock; blood pressure drops to zero; no pulse nor heart sounds detectable; respiratory gasps.

0:06. Electrocardiogram 2. (Ventricular fibrillation.)
0:07. Respiration stopped.
0:08. Artificial respiration instituted; animal placed in shock position and abdominal binder applied.
0:10. Ventricular fibrillation continues.
0:20. Blood pressure, zero; no spontaneous respiration.
0:30. Blood pressure, zero; no spontaneous respiration.
0:50. Blood pressure, zero; no spontaneous respiration.
0:51. Blood pressure, zero; no spontaneous respiration. Ventricular fibrillation ceases.
0:51. 0.5 cc. of 1 to 1000 epinephrin injected into femoral vein; 2 cc. 6 per cent glucose wash.
0:52. Extrathoracic manual massage. No cardiac response.
0:56. 1 cc. of 1 to 1000 epinephrin injected into femoral vein.
0:58. Slight cardiac response.
1:00. Regular coördinate heart beat. Blood pressure rapidly elevated to 90 mm. Hg.
1:02. Blood pressure falling.
1:03. Infusion of 1 to 50,000 epinephrin in 6 per cent glucose solution into femoral vein.
1:03. E. K. G. (Rapid coördinate beat.) Spontaneous respiratory gasps.
1:08. E. K. G. (Normal rate and rhythm.) This was followed by normal, spontaneous breathing, and a return of the reflexes, consciousness and voluntary movements.

SERIES III. Eighty-two animals (53 cats, 29 dogs) were used to develop the best plan of reëstablishing and maintaining an effective circulation and respiration. The measures already described are incapable of inaugurating or maintaining an efficient circulation; they do, however, retard the dissolution of the vital centers. A cardiac excitant is called for. The extremely consistent stimulatory effect of epinephrin on the accelerator-augmentor mechanism of the heart, and its beneficial pressor effect on the circulation strongly favor its use in resuscitation. The entirely satisfactory results we obtained with this sympathomimetic amin made it unnecessary for us to experiment with any substitute. The dose and the site of injection most likely to restore the circulation had to be determined. Concentrated solutions of epinephrin injected directly into the heart or into a vessel close to the heart often produce untoward phenomena, such as acute cardiac dilation, pulmonary edema, and ventricular fibrillation. Both for effectiveness and convenience, the most satisfactory site for injection was found to be a peripheral vein. Either the saphenous or femoral vein was used in the majority of our experiments. The intensity of the action of epinephrin varies with the state of the vascular system; when the latter is depressed, larger doses are required to elicit a given effect. Volatile anesthetics depress the circulation and diminish its response to epinephrin. In many of our experiments, as much as 0.1 cc. of 1 to 1000 epinephrin per kilo was required to arouse the heart and restore the circulation of animals overdosed with ether, chloroform or electric shock. In many cases, such an amount may prove

excessive; therefore, half this dose is advisable as the initial injection. If there is no response in three minutes, double this amount is introduced into the vein. Exceptions to the use of relatively large doses of epinephrin are a myocardium damaged by chloroform. The rise of blood pressure produced by excessive doses of epinephrin may be great enough to overburden the damaged cardiac muscle, and cause acute fatal dilatation of the heart.

During cardiac arrest the circulation is at a standstill; a minute quantity of epinephrin injected into a peripheral vein is not carried to the heart by the natural circulation; it must be forced into the heart by the rapid injection of a small quantity of fluid. A wash of 3 cc. of fluid in the cat, and of 10 cc. in the dog was found adequate to drive the epinephrin to the heart. Emptying of the veins by their massage toward the heart assisted the movement of the epinephrin. Rhythmic manual compression of the chest wall causes indirect massage of the heart, and forces the blood with its epinephrin through the coronary bloodvessels. In the "dead" animal, compression of the chest wall causes a rise of blood pressure demonstrable on a mercury manometer; the release of this pressure is followed by the return of the mercury to the zero level. This reaction is markedly modified after an effective dose of epinephrin has been administered. Compression of the chest wall then results in a considerably increased excursion of the manometer, and, on the release of the compression, the mercury in the manometer no longer falls to the zero line. When this phenomenon has been achieved, the return of cardiac pulsation is imminent. The initial response of the circulation to the minimal effective dose of epinephrin is a rise of blood pressure to slightly above the normal. When necessary, an efficient circulation is maintained by means of an intravenous infusion of 6 per cent glucose solution, with or without the addition of very minute doses of epinephrin. The rate of the infusion is governed by the fluctuations of the blood pressure. A decided fall of the blood pressure demands an acceleration of the rate of infusion (which, however, should never exceed 3 cc. per minute), and the cautious administration of epinephrin.

If a satisfactory blood pressure is maintained, no further treatment is required except the continuance of the artificial respiration. However, if the blood pressure tends to fall below the normal level, means must be taken to prevent a serious decline. Physiologic saline and Ringer's solutions were tried, but we found neither as satisfactory as 6 per cent glucose. Our routine was to start a slow intravenous infusion of glucose, as soon as the blood pressure fell below the normal level. If glucose failed to maintain the blood pressure at a satisfactory height, small doses of epinephrin were administered repeatedly, or small amounts were added directly to the glucose solution and run into the vein. We consider it important to maintain the blood pressure at an approximately normal level,

avoiding excessive doses of epinephrin. Not only does epinephrin stimulate the heart, and raise blood pressure, but Schmidt and others have demonstrated the advantages of epinephrin as a respiratory stimulant.[3,4] Our experimental findings tend to corroborate their views. After the reinstatement of an effective circulation an additional injection of epinephrin would often produce a marked rise of blood pressure which was immediately followed by spontaneous breathing.

Depending on the condition of the animal, a variable length of time elapsed between the restoration of the circulation and the appearance of spontaneous respiration. Artificial respiration is interrupted at intervals to ascertain when voluntary inspiratory gasps occur; it is then cautiously discontinued until normal respiratory movements take place, when it is permanently stopped. Natural breathing is followed by a rapid return of the reflexes, and subsequently of voluntary movements and of consciousness. Sometimes it is impossible, with the known means, to reinstate the respiration, even after a normal circulation is established. We are therefore making a comparative study of respiratory stimulants.

Summary. The order of treatment that proved most reliable in resuscitating animals killed by ether, chloroform or electric shock may be summarized as follows:

Place the animal immediately in shock position. Begin artificial respiration by manual compression of thorax until the trachea is catheterized or cannulized. Mechanical artificial respiration is then instituted. Apply the abdominal binder. These procedures require not more than 2 or 3 minutes. Expose and cannulize the femoral vein, and connect it with the glucose reservoir. Inject epinephrin into femoral vein, and wash it to the heart by a small amount of glucose. Reinforce artificial respiration and massage heart indirectly by manual compression of the thorax. If the heart does not recover within 3 minutes, the epinephrin and glucose are repeated. After the heart has begun to beat, blood pressure is maintained at a proper level by the slow intravenous drip of glucose, with or without epinephrin. Artificial respiration is reduced to a suboptimal level; when the animal gasps, artificial respiration is stopped and circulation is supported, if necessary, until consciousness is regained.

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THE SIGNIFICANCE OF THE BARGEN ORGANISM AS AN ETIOLOGIC FACTOR IN ULCERATIVE COLITIS.*

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In spite of the fact that Bargen[1] states that the probable etiologic factor in ulcerative colitis is a Gram-positive, lancet-shaped diplococcus which he has recovered after direct proctoscopic examination in 80 per cent of 68 cases, the bacterial etiology of this condition is still a matter of dispute. He also says that the organism can only be obtained by direct proctoscopic culture taken from the depths of an ulcer of the colon after the latter has been thoroughly cleansed by repeated washings and the top of the ulcer has been carefully wiped. Furthermore, cultures of stools failed to yield the organism, though it predominated in cultures of the rectal discharge of mucus, pus and blood. The Bargen organism has certain distinct cultural and fermentative characteristics. The material obtained during proctoscopic examination is immediately cultured in warm dextrose brain broth,[2] blood agar and lactose agar and incubated for 24 hours. The organism thus isolated is a Gram-positive lancet-shaped diplococcus growing in twos and fours. A capsule has been observed, thus morphologically the organism resembles a pneumococcus. It is not bile soluble.

In view of the conflicting opinions that have been expressed regarding the significance of the Bargen organism in ulcerative colitis, it was thought of interest to study the stools and proctoscopic scrapings in a group of 314 patients suffering from a variety of conditions. Approximately 20 per cent of the cultures were from material obtained during proctoscopic examination while in the remaining 80 per cent, cultures were made directly from the feces. Cultures of 4 stomach and 1 duodenal contents were also made. Bargen's technique was followed, and in addition we streaked progressive dilutions on agar plates. The best results were obtained by following the Bargen technique.

Statistically considered, the Bargen organism was encountered twice in 30 proctoscoped cases of ulcerative colitis. In this group, though definite evidence of ulceration was found and cultures were taken from ulcerated areas, no deep extensive lesions were seen. In

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111 cases of spastic colitis of which 22 were proctoscoped and cultures made, and in 89 had stool cultures made, the Bargen diplococcus was found twice. In these cases no ulcers were revealed by proctoscopy. The Bargen organism was recovered from 2 of the 22 proctoscoped culture cases. In the group of 173 miscellaneous cases of which 25 were healthy individuals and the remaining 148 suffered from a variety of diseases, 20 per cent of the cultures were taken from material obtained during proctoscopy. These cultures were entirely negative for the Bargen organism which was only recovered once in the miscellaneous group, and then from the stool of a patient with chronic arthritis having no history or clinical evidence of ulcerative colitis. The typical heat-resistant enterococcus was isolated from 306 cases in the entire series of 314 cases. (See Tables 1 and 2.)

This table shows the varying fermentation reactions of different strains of the enterococcus and the Bargen diplococcus, without any essential differences between the two types.

TABLE 1.—FERMENTATION REACTIONS.

200 STRAINS OF THE ENTEROCOCCUS.

	Lactose.	Saccharose.	Dextrose.	Mannite.	Maltose.	Inulin.
90 strains	+	+	+	−	+	−
63 strains	+	+	+	−	−	−
19 strains	+	+	+	+	+	−
28 strains	+	+	+	+	−	−

6 STRAINS OF THE BARGEN DIPLOCOCCUS.

	Lactose.	Saccharose.	Dextrose.	Mannite.	Maltose.	Inulin.
4 strains	+	+	+	−	−	−
2 strains	+	+	+	+	−	−

+ = Acid − = No reaction.

TABLE 2.—DISTRIBUTION OF ENTEROCOCCUS AND BARGEN DIPLOCOCCUS.

30 ULCERATIVE COLITIS CASES.

Feces Cultures
None made

Protoscoped Cultures, 30
Enterococcus, 28
Bargen diplococcus, 2

111 SPASTIC COLITIS CASES.

Feces Cultures, 89
Enterococcus, 89
Bargen diplococcus, 0

Protoscoped Cultures, 22
Enterococcus, 20
Bargen diplococcus, 2

173 MISCELLANEOUS CASES.

Feces Cultures, 132
Enterococcus, 123
Bargen diplococcus, 1
No enterococcus or Bargen, 8

Protoscoped Cultures, 36
Enterococcus, 36
Bargen diplococcus, 0

Stomach Cultures, 4
Enterococcus, 0
Bargen diplococcus, 1

Duodenal Contents Cultures, 1
Enterococcus, 0
Bargen diplococcus, 0

In 1 specimen of stomach contents cultured, from a case of carcinoma of the cardiac end of the stomach, an organism corresponding in

all respects to the Bargen diplococcus, was recovered. Stool cultures of the same case did not reveal this organism.

The results which have been presented in the previous paragraphs are at considerable variance with those recorded by Bargen. Gram-positive lancet-shaped diplococci found in cultures taken as previously described have also been called Micrococcus ovalis, Enterococcus and Streptococcus fecalis[3] and must be differentiated from the so-called Bargen strain by more than microscopic appearance. We experienced no difficulty in isolating the Bargen organism in the cases in which it was found, either by plating after preliminary culture in dextrose brain broth, or by fishing the small colonies from successive streaked plates. We do not believe, therefore, that in the series of ulcerative colitis cases the Bargen diplococcus was present and not recovered because of some technical error. We were also able to isolate the Bargen organism from occasional cases of nonulcerative colitis. No organism was classified a Bargen diplococcus unless it corresponded to the cultural, fermentative and heat-resistant characteristics described by Bargen.

In our experience the enterococcus is practically a constant inhabitant of the colon. All of the strains recovered by us fermented lactose, dextrose and saccharose, while there was no constancy as to their reaction on mannite or maltose. The Bargen diplococci, when isolated, were found to have similar sugar reactions to the enterococci.

The strongest point in differentiation between the enterococcus[4] and the Bargen diplococcus is the heat-resistance test. The enterococcus is still viable at the end of one hour of heating to 60° C., while the Bargen strain is killed at the same temperature. The Bargen diplococcus seems to be representative of a number of strains of the enterococcus group.

In a series of animal experiments Bargen[5] injected 169 rabbits intravenously. Of these animals 56 developed lesions and only 11 of the 56 had received intravenous injections of the Bargen organism. The other 45 had received mixed cultures of a Gram-negative bacillus ("in all essentials a colon bacillus"—Bargen does not definitely identify this organism) and the Gram-positive diplococcus. To quote Bargen, "The lesions in the main were more extensive and the diarrhea more severe in those that had received mixed cultures of the Gram-positive diplococcus and the Gram-negative bacillus."

We have repeated Bargen's animal work on a much smaller number of animals. Five rabbits which were fed on a normal diet were injected as follows: 2 received intravenous injections of 4 cc. of a 24-hour dextrose brain broth culture of the Bargen diplococcus, and 2 a 24-hour culture of the enterococcus. The fifth rabbit was kept as a control. The injected rabbits remained healthy, gained weight and at no time showed evidence of diarrhea or other symptoms. At autopsy, 4 weeks after injection, they showed no gross anatomic or microscopic lesions.

In another experiment 10 rabbits were fed for 2 weeks on vitamin-free food (crushed autoclaved oats and water) according to the method of McCarrison.[6] Four of these rabbits were then injected intravenously with 5 cc. of a 24-hour dextrose brain broth culture of the Bargen diplococcus and 4 rabbits were similarly injected with 5 cc. of the enterococcus. Two were kept as controls.

None of these injected rabbits exhibited any diarrheal symptoms. Two of the 4 injected with the enterococcus died 10 days after injection, apparently from starvation as did also one of the control animals. The remaining 7 rabbits showing loss of weight and symptoms of malnutrition still being alive at the end of 3 weeks from the time of injection, were then killed and autopsied. In none of these 10 rabbits was there any evidence of intestinal ulceration or gall bladder disease and neither gross anatomic or microscopic sections of the organs showed any significant lesions. Bargen,[1] injecting 9 rabbits that had been fed on a vitamin-free diet ("crushed oats and water or autoclaved rice, according to the method of McCarrison") with 5 cc. of dextrose brain broth culture of the Bargen diplococcus, was able to demonstrate lesions in the colon. Of these 9 rabbits all were dead within 5 days. Eight had lesions of the colon ranging from submucous hemorrhages to minute ulcers, and 3 of the 8 had empyema of the gall bladder.

We do not believe that the work reported by Fradkin and Gray[7] has any clinical significance due to the huge amount of organisms (40 to 50 cc. dextrose brain broth cultures of the Bargen diplococcus) injected intravenously into their animals over a period of from 5 to 7 days. Furthermore they do not mention using any control animals or control organisms.

Torrey,[8] in a personal communication to one of us, expresses the same opinion, that the Bargen diplococcus seems to be an atypical member of the enterococcus group.

Conclusions. The Bargen diplococcus is a strain of the enterococcus group. It is not regarded as the specific factor in ulcerative colitis since it is not found in every case of this disease and in our experiments not even in a majority of the cases. It can be recovered from cases showing no ulcerative lesions of the colon.

The Bargen organism was recovered in cases of ulcerative colitis and nonulcerative colitis; from the stomach contents of a patient with gastric carcinoma and from the stool of a patient with chronic arthritis.

The clinician should remember that every Gram-positive, lancet-shaped diplococcus reported found in the stools or from proctoscopic cultures is not necessarily a Bargen organism. Fermentation reactions, and most important of all, the heat resistance test must be employed before the identification can be made.

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A CONTRIBUTION TO THE PATHOGENESIS AND HEREDITY OF THE LAURENCE-BIEDL SYNDROME (DYSTROPHIA ADIPOSOGENITALIS, RETINITIS PIGMENTOSA, MENTAL DEFICIENCY AND POLYDACTYLISM).

Report of Three Cases in One Family.

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Dystrophia adiposogenitalis, or Froehlich's syndrome of obesity and hypogenitalism, is well recognized. It is usually referred to as a state of hypopituitarism, signifying that the pituitary gland is at fault. In support of this idea are the many instances of pituitary tumors producing this symptom complex. On the other hand, the syndrome occurs in cases where there is no recognizable hypophyseal disorder *per se*. In this category belongs the familial form of Froehlich's dystrophy associated with other hereditary and congenital defects, such as retinitis pigmentosa, mental deficiency and polydactylism. For this clinical picture the name of Laurence-Biedl syndrome was suggested by Solis-Cohen and Weiss.[5] The constancy of the association of these phenomena is of striking interest because it suggests that obesity and genital atrophy may be inherited genotypic defects, as are the other anomalies found in this condition, namely, supernumerary fingers and toes, retinitis pigmentosa and mental deficiency. Since the latter 3 conditions occur as isolated defects it may be possible that obesity, with or without genital deficiency, may also occur as a single inherited genotypic defect. It is the purport of this communication to add

3 cases of this syndrome to the 42 recorded in the literature and to discuss the pathogenesis and heredity of the disordered mechanisms.

The first paper on the subject appeared in 1866 by Laurence and Moon,[1] in which they describe 4 members of 1 family who showed pigmentary degeneration of the retina, adiposity, genital dystrophy and mental deficiency. Three of the cases showed imperfections of bony and muscular development producing defects in gait. The authors compared the patients to cretins because of their mental deficiency and they recognized the retinal changes as but a part of a general developmental failure.

In 1920 appeared the thesis of Georges Bardet[2] on a syndrome of congenital obesity associated with polydactylia and pigmented retinitis, in which he describes the case of a girl aged 11 years. He also reviews a case report in 1898 by DeCyon and refers to 2 cases in brothers reported in 1913 by Farnes. Bardet concluded that this syndrome was due to a lesion of both lobes of the pituitary gland during the period of embryonal or fetal development.

Biedl's paper[3] in 1922 discusses the syndrome as a distinct one and characterizes it as consisting of obesity, genital hypoplasia, atrophy of the optic nerve with pigmental degeneration of the retina frequently of atypical form, with hemeralopia or night-blindness, polydactylism and inhibition of the mental processes. Two cases in a brother and sister are reported, both having all of the aforementioned symptoms. Four other members of the same family were normal; 2 others died in infancy, both of whom showed polydactylism and who might have shown the complete picture had they lived. A third case in another family is referred to. Biedl states that since the Roentgen films of the sella turcica were normal, the disease is not of hypophyseal origin properly speaking, but of cerebral origin, the lesion being a disturbance of development of the diencephalon in the region of the infundibular area. In 1924 Raab,[4] from Biedl's Clinic, using the above cases of Biedl in a consideration of hypophyseal and cerebral obesity with genital atrophy, discusses the physiopathology from a mechanical standpoint. He envisages a functional unit in the form of a hypothalamic-infundibular-hypophyseal complex, in which the pars intermedia of the pituitary gland furnishes a secretion. The secretion passes through the posterior lobe and the infundibular stalk to the floor of the third ventricle where certain metabolic and genitotrophic centers are energized. The mechanical factor is in the form of an obstruction to the flow of the secretion through the stalk by an unusually high or massive dorsum sellæ. He states that Biedl has referred to this factor as a strong possibility in the production of cerebral obesity and genital atrophy. He considers the dorsum sellæ defect as a skeletal anomaly similar to that of polydactylism. In addition to this theory Raab considers two others, namely, congenital hypoplasia of the hypophysis and internal hydrocephalus.

From their impressions of the above-mentioned literature and personal contact with Biedl, Cohen and Weiss,[5] in 1925, proposed the name of the Laurence-Biedl syndrome. They recorded 4 cases in one family of 8, who exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the affected children showed polydactylism; the eye grounds showed a typical retinitis pigmentosa. In their discussion they state that an hypophyseal lesion cannot be proved; that Roentgen ray examinations of the sella region do not show conclusive changes. No anomaly of osseous development is found (except polydactylism). Sugar tolerance tests do not indicate pituitary disease. Basal metabolic studies were below normal in 3 of the children. Parents and children gave negative Wassermann reactions. Cohen and Weiss refer to Raab's ideas as most attractive, but prefer to keep an open mind on the pathogenesis of the syndrome until more conclusive evidence is presented.

Bernhardt,[6] in 1928, states that only about 20 positive observations of this syndrome have appeared in the world's literature. He reports 2 new cases in brothers aged 16 and 10 years respectively. Both boys had visual impairment from the age of 18 months and a Froehlich's type of adiposity with hypogenitalism. One had polydactylism and a permanent severe nystagmus; the other a pronounced tower-shaped skull, unilateral cryptorchidism, genu valgum and severe nystagmus. The latter also had positive evidence of a moderate degree of diabetes insipidus. Sellar Roentgen rays were negative; basal metabolic rates were normal. In the summary he states that these cases present a primary disturbance of development, the principal seat of which must be looked for in the hypophysis, midbrain and optic nerve region complex. In accord with Biedl, he considers this syndrome as a special case of the so-called cerebral form of the Froehlich adiposogenital dystrophy. He mentions a case report of von Jaksch in 1912.

In the same year appears Boenheim's[7] contribution in which he adds to the cardinal characteristics of the syndrome, hardness of hearing, malformations other than polydactylism, and perhaps cutaneous pigmentation. He states that psychical disturbances belong to the classical picture, especially in the form of dementia, and were observed by him in some of the cases, whereas in others it was absent. Boenheim accepts the tenets of Biedl and Raab as probable causative factors. He reports 4 cases, 2 of which were familial. One brother had adiposity, polydactylism, arrest of mental development and acromegalic tendencies of the hands and feet; he was aged 28 years. The other brother, aged 36 years, had hemeralopia with retinitis pigmentosa, genital hypoplasia, mental retardation, but was small and slender. The author remarks that the entire clinical picture in these 2 cases could be elucidated only through connection of each case with the other.

A third paper appeared in 1928, that of Ricaldoni and Isola.[8] Four more cases are described in one family ranging in age from 12 to 21 years. All of the cardinal manifestations were present in the 4 cases and the impaired vision began in each one at a very early age. In 1 child there was a moderate degree of hemiatrophy of the entire body. All 4 were very timid, very emotional and of poor intelligence. Serologic and urine tests were all negative. Roentgenograms of the skulls in all 4 patients showed a small sella turcica with very long clinoid processes covering the sella like a roof. There was no retardation of ossification or fusion of the epiphysis of the long bones. The family history was very interesting. The parents were first cousins and apparently healthy. Ancestrally, there were several blind individuals in the maternal line and several obese ones in the paternal line. There were 4 unaffected children in the present family, but 1 died seven days after birth and had an imperforate anus; another had a distended abdomen and died 2 days after birth; a third was a stillbirth. The authors, judging from the smallness of the sella turcicas, reason that the lesion is in the hypophysis. But, they say, if the malformation of the sella was the primary cause of the condition, it would have been found in the other reported cases, and this has not always been true. They emphasize the familial character of the disease and say that direct transmission of the syndrome has not been seen because the patients are almost all of necessity infertile. It is their opinion that the adiposogenital dystrophy is the primary and necessary symptom of the syndrome; the retinitis and polydactylia are not necessarily present and that there are formes frustes without one or both of them. The most incomplete form is that with adiposogenital dystrophy alone, which is a dysplasic congenital form of the dystrophy as opposed to the purely accidental type of Froehlich-Babinski. And one of the characteristics of the congenital form is that it is usually associated with retinitis and polydactylism, showing that it is embryonic in origin, while accidental dystrophy is generally accompanied by symptoms showing irritation or compression of the brain or the region adjacent to the hypophysis.

A paper by Rieger and Trauner,[9] in 1929, is entitled "A Case of Biedl-Bardet Syndrome and the Hereditary Relations of This Condition." Their case presents in brief the following features: A girl, aged 6 years in 1925, showed marked adiposity, retinal degeneration and hyperdactylia, infantile genitalia, normal mentality, hyperextensibility of the wrists; medium-sized normal sella. Consanguinity in the parents is present. An older child developed multiple sclerosis; a younger one died at 6 months, was fat and had a supernumerary toe. A number of fat people exist in both branches of the family. These authors do not accept the theory of hypophyseal secretory disturbance of previous authors, nor that of cerebral

disease with primary changes in the skeleton expounded by Biedl and Raab. They believe the disease is genotypic in nature. This is confirmed by the fact that in each case the three main symptoms of the syndrome are characteristic, each one of them being of an hereditary nature.

deSchweinitz,[10] in his Bowman lecture, speaks briefly of the association of pigmentary degeneration of the retina with pituitary diseases and polydactylism. He mentions 3 cases of this character that he has himself observed. A case of Chaillous[11] is interesting because a girl, aged 4 years in 1914, with enormous obesity, polydactylia and defective vision, had normal eye grounds, but in 1919 the evidence of retinitis pigmentosa was found. Roentgen ray of the sella was normal. Chaillous mentions a case reported by Bertolotti in 1914. McAlpine[12] describes a case of a boy aged 16 years, showing all of the characteristic phenomena. A brother and sister affected by this condition are reported by Beck;[13] and Lisser[14] reports the case of a girl, aged 8 years

Serejski,[15] contributing to the Biedl Jubilee number dedicated to Dr. A. Biedl on the occasion of his sixtieth birthday, writes of the Laurence-Biedl syndrome and reports a case. He attempts to include this syndrome in the same group of heredodegenerations in which amaurotic family idiocy belongs. Other case reports have been made by Denzler,[16] Deusch,[17] Lange[18] (4 cases), von Ratner[19] and Bauer.[20] In the ancestry of Deusch's case, a paternal uncle had polydactylism and several others in the father's family exhibited adiposity.

Report of Cases. CASE 1. There are 6 children in this family, 3 of whom are affected with the condition under consideration: Milford, aged 12 years, the second born; Margaret, 2½ years, the fifth born; Helen, 1½ years, the last born. They are very obese, mentally retarded and hemeralopic, but they do not have polydactylism. The birth was uneventful in each instance and there occurred no infectious illness or convulsions in infancy.

Milford weighed 8 pounds at birth and at 3 months weighed about 10 pounds more than he should. At this age he apparently observed objects as a normal child and did not manifest evidence of impaired vision until about the fifth year. Gain in weight has been constant, at present he weighs 140 pounds. Visual impairment is very marked and he has the symptom of night blindness (hemeralopia). He can read ordinary print, holding the page about 8 inches away, but only in bright daylight. He has no difficulty in finding his way in daylight or in a brightly-lit room, but on entering a dimly-lit corridor he gropes about because he cannot discern objects about him. It goes without saying that he has the greatest difficulty in finding his way at night. He is mild-mannered, quite stable emotionally but is mentally retarded, lacking the spontaneity and ready responsiveness of a boy aged 12; there is no qualitative mental defect, however. Evidence of polyuria, polydipsia or excessive appetite is lacking. (Figs. 1 and 2.)

The obesity is of the Froehlich type. The abdomen is rounded and protuberant with increase of girdle and suprapubic fat. The breasts are very prominent; the proximal portions of the extremities are well-rounded as in the female and there is a marked degree of genu valgum and pes planus.

The genitals are extremely underdeveloped and truly infantile; the scrotum is very small and without the normal contents; testes could not be palpated in the inguinal canals. There is not a trace of axillary or pubic hair. Pupils and extraocular movements are normal but with a fine nystagmus laterally. The optic disks are grayish; the vessels of the fundus are reduced in size.

FIG. 1.—Case 1. Showing Froehlich type of adiposity.

The retinæ show a pigmentary degeneration of atypical character with uncovering of the choroidal circulation. Vision is O. S. 5/100, O. D. 5/150. The sella turcica is normal in all respects, measuring 10 mm. by 6 mm. The deep and superficial reflexes are normal. The blood and urine studies were entirely negative; sugar tolerance test and basal metabolic rate were normal. Water intake and output were not abnormal and blood Wassermann was negative.

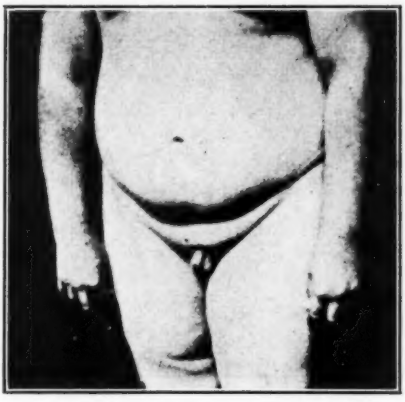

FIG. 2.—Case 1. Showing hypogenitalism.

CASE 2. In Margaret the visual defect was suspected and looked for earlier because of the parents' experience with the first case. It was noted that in the third or fourth week after birth the child's visual attention could not be held and that its eyes flitted about more than in the normal children

and that the pupils were very large. She slept more than did the normal children. She has not learned to walk. The obesity is extreme, the fat hanging in folds around the trunk and limbs. Margaret is so unwieldy-looking that one is not surprised to hear that she prefers to remain in a sitting posture for hours rather than move. There is a definite mental

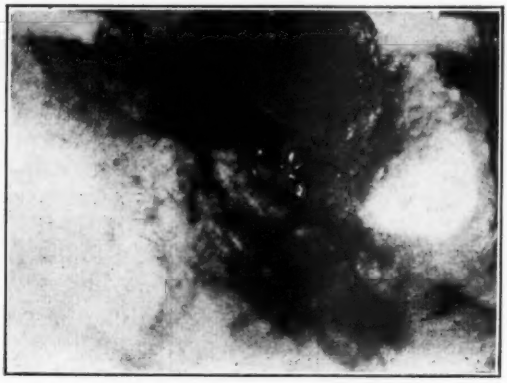

FIG. 3.—Roentgen ray of sella turcica in Case 1, showing no gross deviation from normal.

defect recognizable even at this early age. She is afraid of strangers and becomes panicky when approached or spoken to. She will not answer except when one refers to food, then she will nod her head. Her appetite is excessive and the intestinal evacuations are almost of adult quantity. Polyuria and polydipsia are not present. The retinal and optic nerve

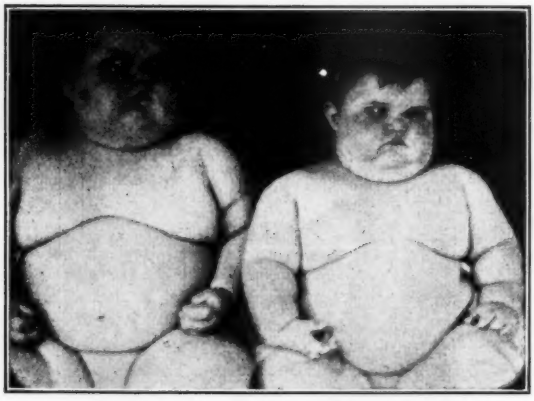

FIG. 4.—Cases 2 and 3.

changes are similar to those present in Milford. A moderate nystagmus is observed; sella turcica is normal and all blood and urine studies are negative.

CASE 3. The visual defect in Helen was observed from birth and it is stated that her eyes were more restless than in the other two. The pupils were dilated from birth. The atypical retinitis pigmentosa is also present.

Her adiposity is even greater than that of Margaret. At 12 months she looked like a 2-year-old because of her size. The fat hangs in folds about her body and limbs. The same mental and emotional defect is observed as in Margaret. The clinical studies were also negative as in the other 2 cases. The question of genital development could not be determined in the younger cases at their present ages. Their vision could not be tested for the same reason. Roentgen examination of all 3 cases showed no change in osseous development. No other congenital anomalies or defects were observed. (Fig. 4.)

The 3 normal siblings are a 15-year-old boy who is small in stature and not fat; a 10-year-old girl, normal in size, vision and intellect; a 5-year-old boy, light in weight. The family history is interesting in that several paternal ascendants have been overweight and tall; a grand uncle weighed 338 pounds and was 6 feet tall; the grandfather weighed 190 pounds and 4 grand aunts and uncles each weighed about 200 pounds. But no one had visual, mental or developmental defects. There is no consanguinity in the parents.

Discussion. From a critical review of the literature one is impressed with the fact that all of the observers are agreed that the syndrome of Laurence-Biedl is an hereditary and familial disorder. That the symptoms of hemeralopia (retinitis pigmentosa), the polydactylism, the feeble-mindedness and the less frequent anomalies reported are unquestionably inherited defects of genotypic character. But unanimity of opinion as to the nature of the adiposogenital dystrophy is lacking. It was natural for the earlier observers to look to the hypophysis for the explanation, namely, Bardet: a lesion of both lobes of the pituitary gland during the period of embryonal or fetal development. Since the roentgenographic sella turcica findings have not been grossly or constantly abnormal except for the occasional finding of a massive and high dorsum sellæ, Biedl and Raab did not feel that the hypophysis was at fault. Instead, they suggested a dysfunction of the hypothalamic region due to the failure of the secretion of the pars intermedia of the hypophysis to reach the floor of the third ventricle to energize certain genitotrophic and metabolic centers because of compression and obstruction of the infundibular stalk by the high and massive dorsum sellæ. Thus Biedl differentiated between a pituitary type and a cerebral (hypothalamic) type of Froehlich's adiposogenital dystrophy. The anomaly of the dorsum sellæ was considered as another expression of defect in the skeleton as the polydactylia. Timme[21] has expressed a similar thought when he stated that "such an anatomical characteristic, as defective conformation of the base of the skull, can be much better understood as being a unit factor in inheritance than can the complicated biochemical process leading to the superficial picture we see."

This theory is not sufficiently impressive to be accepted without further analysis. If the osseous anomaly be the unit factor conditioning the appearance or nonappearance of the fat and genital dystrophy, then the occurrence of the latter would not be so constant

a feature of the syndrome, because the dorsum sellæ is as often normal in these cases as it is abnormal. Also, sella malformations should in some instances interfere with the function of the entire hypophysis and occasionally produce other types of dyspituitarism such as dwarfism, gigantism or acromegaly which, however, are not parts of the Laurence-Biedl picture. Therefore, one must look to regions which characteristically give rise to disturbances of fat metabolism and hypogenitalism, namely, the hypothalamic region of the diencephalon.

In certain cases following epidemic encephalitis, dyspituitary syndromes—excessive adiposity, increased carbohydrate tolerance, genital dystrophy—are sometimes observed. The pathologic evidence that the pituitary gland is ever involved in epidemic encephalitis is very slender. On the other hand, with the well-known predilection of the virus of epidemic encephalitis to involve the gray matter of the midbrain, the nuclei of the hypothalamus might well be involved. Urechia and Elekes[22] examined the brain of a case of adiposogenital dystrophy with polyuria and found a marked internal hydrocephalus and sclerotic foci of an old encephalitis in the hypothalamus. The hypophysis was normal while the tuber cinereum was compressed and thinned by the intraventricular tension, and the nuclei of this region showed marked cellular lesions.

Recent research has indicated that many symptoms formerly ascribed to a lesion of the pituitary body itself may result from lesions involving the closely related hypothalamic region of the brain. Camus and Roussy[23] claim to have produced typical dyspituitary syndromes in dogs by injury to the tuber cinereum above the pituitary glands, the latter being left intact. Similar results were obtained by Aschner[24] and Bailey and Bremer[25] indicating, as first suggested by Erdheim, that a disturbance of the hypothalamus may be the cause of many of the symptoms attributed to pituitary derangement. Roussy[26] states that certain tuber nuclei regulate the fat, others the sugar and water metabolism; their lesion is followed by Froehlich's syndrome, which could not be produced by removing the hypophysis without a lesion of the tuber cinereum. In his experiments on 149 dogs and 46 cats, Roussy has checked up earlier publications and has found new facts which support his conception of the rôle of the vegetative centers of the region of the tuber cinereum.

The occurrence of obesity after experimental lesions confined to the hypothalamus has been observed by many workers. Gournay and LeGrand present evidence that the paraventricular nucleus is the structure damaged in animals developing obesity. Genital atrophy is usually associated with obesity which results from a hypothalamic lesion. Camus and Roussy contend that obesity never results from a lesion confined to the pituitary gland, but is always due to a lesion of the tuber cinereum, but as Cushing points

out, it is difficult to believe that the obesity associated with a pituitary tumor which remains absolutely confined within its dural capsule can possibly be produced in this way. Cushing and Maddock have shown that adiposity can be produced by obstructing the infundibulum.

In this somewhat controversial situation, Collin[27] warns that, in his opinion, the overestimation of the vegetative centers in the hypothalamus without taking into consideration their correlation with the hypophysis will prove as one-sided as was the former endocrinologic point of view. This advice is particularly striking when we recall that the posterior lobe of the pituitary is developmentally a protrusion of the tuber cinereum, and that in the fully-developed animal nerve fibers are seen running from one to the other. It becomes, therefore, a justifiable speculation to consider both as parts of the same complex neuroglandular mechanism. If, therefore, the hypothalamus becomes, in certain instances, the seat of an embryonal developmental defect, then it is reasonable to expect a dysfunction of the neuroglandular complex under consideration.

The adiposogenital dystrophy of the Laurence-Biedl syndrome is of this order, the embryonal defect involving the diencephalon. In the development of the nervous system each stage is identified with the activity of certain specific genes. The genes concerned with the evolution of the ventral portion of the ectopic zone of Schulte surrounding the optic vesicles which gives rise to the hypothalamus, are abnormal. They are transmitted through the germ plasm and produce an inherited diencephalic defect as a unit character.

The almost constant association of retinitis pigmentosa and feeble-mindedness with the Froehlich syndrome in the Laurence-Biedl picture is explained on this basis of a genetic defect of the prosencephalon. In the early stages of the neural tube the first segment of the encephalon is the forebrain (prosencephalon). This division of the brain develops two large evaginations, the optic vesicles, from which are derived the retinæ of the eyes. A narrow, circumferential area of the forebrain surrounds the optic vesicle on its dorsal, cephalic and ventral aspects and is called the ectopic zone, from the three areas of which the end brain together with the several parts of the interbrain take on form. From the dorsal area develop the epithalamus, thalamus, subthalamus and geniculate bodies of the diencephalon. From its ventral area the hypothalamus takes origin. The cephalic area of the ectopic zone gives rise to the end brain.

The optic vessels gradually become the optic cup and stalk which retains connection with the ventral segment of the ectopic zone. The stalk eventually serves as the framework through which the developing fibers of the ganglion cells of the retina pass to form the optic chiasm. The remainder of the ventral segment of the

ectopic zone gives rise to the other chief constituent of the hypothalamus, namely, the infundibular region from which differentiates the tuber cinereum including the bulbous infundibuli, infundibular process and stalk, the lateral eminences and the postinfundibular eminence (Tilney and Riley[28]).

It is seen, therefore, that the development of the infundibulum, the optic chiasm and the retinal fibers is an intimate one in that the ventral segment of the ectopic zone gives origin to all of them. Therefore, a defect in the character of the genes responsible for the laying-down of the various steps in the evolution of the ectopic zone in its ventral segment may result in an abiotrophic condition of the infundibulum, optic nerves and retinæ. The infundibular defect results in the Froehlich picture, the chiasmatic defect produces the optic atrophy, and the pigmentary degeneration of the retina is explained not by abnormal ganglionic-cell development but through involvement of certain fibers in the optic chiasm. The authority for this statement is the following from Tilney and Riley:[29] "Not all of the fibers of the optic chiasm are afferent in their course, some being efferent from the visual cortex as well as from the superior colliculi. To these fibers has been attributed the function of governing chemical changes which occur in the retina and also movements in certain elements of the retina, the retinal pigment cells." Ranson[30] states that "the optic nerve also contains some efferent fibers which terminate in the retinæ. (Arey, 1916.)"

Since the cephalic segment of the ectopic zone gives origin to the end brain, it may be that the defect in intellectual development is a part of this segmental embryonic deficiency.

The relatively new sciences of genetics and experimental embryology have advanced positive and inescapable experimental evidence proving that the chromosome is a structure composed of many diverse parts, each part or gene having a definite effect on development and therefore, a definite effect on the characteristics of the individual produced. Much of this evidence has come from the investigations on the common fruit fly, Drosophila melanogaster, the organism whose heredity is best known. It has been found that at least 50 pairs of genes coöperate to produce the normal red color of the eye; if any one of these 50 genes is altered, or is defective, the eye color will be diverse from the normal. The same situation is found for all characteristics. Another defective gene in Drosophila causes the animals to produce reduplicated legs. This is due to a gene in the X-chromosome, so that the abnormality shows sex-linked inheritance. A modified gene in the X-chromosome near its left end, causes the fruit fly to grow to nearly twice the size of ordinary Drosophilas; individuals without this gene do not become giants, no matter how well fed. (Jennings.)[31]

In man, differences in body-build (stoutness and slenderness) are often due to gene differences (Davenport).[32] Structural abnormal-

ities of certain kinds are usually or always due to gene peculiarities such as polydactylia. Therefore, from the viewpoint of genetics, single unit characters such as polydactylia, mental deficiency, obesity, thinness, color blindness, deafness, retinitis pigmentosa, and others, are readily conceived as inherited traits. But when several occur together often enough to be considered as a distinct clinical entity, one must explain the association either as a chance coupling of unit characters or on the basis of a genetic defect involving a developmental center of wider and more far-reaching influence. This is the case in the Laurence-Biedl syndrome. The adiposogenital dystrophy, retinitis pigmentosa and mental deficiency are related to a genetic defect of the ectopic zone in its cephalic and ventral segments; in other words, a cerebral genotypic unit character. The polydactylia, skull deformities, atresia ani and other occasional anomalies are present only through the accidental coupling of somatic genotypic unit characters.

Summary. 1. Adiposogenital dystrophy, retinitis pigmentosa and mental deficiency are the most constant phenomena of the Laurence-Biedl syndrome in the order given; polydactylism is next and other anomalies of development last.

2. This form of Froehlich's dystrophy is considered herein to be a genotypic inherited unit character defect, because the associated symptoms of the Laurence-Biedl syndrome are found occurring as isolated manifestations of the same order.

3. The frequent association of the first three elements of the syndrome is explained on the basis of a developmental defect of the ectopic zone of the prosencephalon, for the embryological reason that the hypothalamus (infundibulum) and the optic chiasm take origin from the ventral segment and the end brain from the cephalic segment of the ectopic zone of Schulte.

4. The other developmental anomalies, namely, polydactylism, skull deformities, atresia ani, and others, appear because of the coupling of somatic genotypic defect characters with the cerebral units characters mentioned above.

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CEREBRAL ADIPOSITY WITH NERVE DEAFNESS, MENTAL DEFICIENCY AND GENITAL DYSTROPHY: A VARIANT OF THE LAURENCE-BIEDL SYNDROME.

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In 1925 Solis-Cohen and Weiss[1] reported 4 children of one family who exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision due to retinitis pigmentosa. Another anomaly, polydactylism, was present in 2. The fat distribution was of the Fröhlich type. Roentgen ray examinations of the sella region did not show conclusive changes nor in any other way could a pituitary lesion be proved. Four unaffected children in the same family were entirely normal.

Search of the literature revealed a remarkably similar family group reported by Laurence and Moon[2] in 1866. Many years later (1922) similar cases were recognized as a syndrome by Biedl.[3] In this and a subsequent communication* he discussed the condition as a familial form of dystrophia adiposogenitalis of cerebral rather than pituitary origin.

Because of the original description by Laurence and Moon and

* Personal communication, 1924.

FIG. 1.—Normal, or possibly slightly smaller than normal sella.

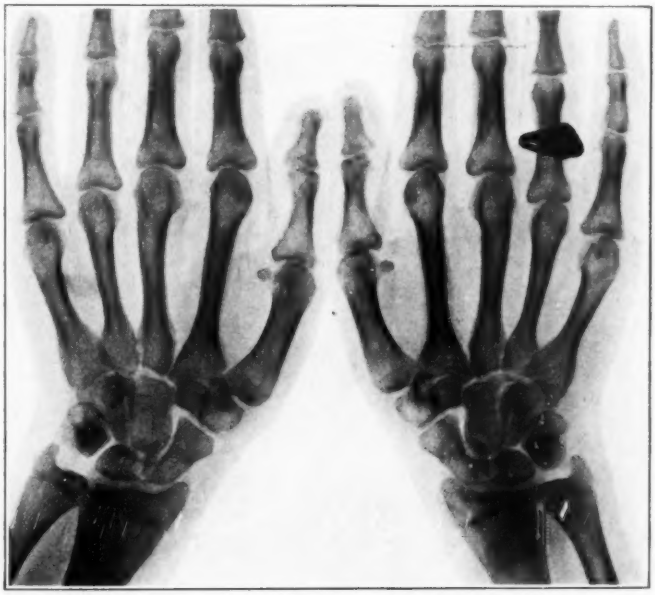

FIG. 2.—Normal osseous development in hands and wrists.

the elaboration as a distinct cerebral obesity syndrome by Biedl the name Laurence-Biedl syndrome was suggested for the condition.

Many cases of the fully developed syndrome have since been reported (the total is now 45), a complete bibliography of which is included in an excellent article by Ornsteen,[4] who adds 3 cases in a contribution to the pathogenesis of the syndrome. Another case recently has been described by McCrae and Weiss[5] and in a separate article made the basis of a discussion of pathogenesis and treatment by Weiss.[6]

The present report has to do with 2 cases in sisters who present cerebral obesity, mental deficiency, nerve deafness and genital dystrophy, apparently a variant of the Laurence-Biedl syndrome, in which deafness takes the place of retinitis pigmentosa.

Case Reports. CASE 1.—C. C., a white girl, aged 16 years, was first observed in 1924 because of defective hearing and retarded growth. She also was troubled at times by psoriasis.

The family history was unimportant except that someone in the father's family was said to have had 6 fingers.

The patient was the youngest of 4 children, born slightly prematurely, but apparently a normal infant at birth. Teething, walking and talking occurred normally. She had chickenpox, measles and occasionally a head cold, but never suffered from sore throat. When the child was about 6 years of age the mother noted that the hearing was poor and an adenoid operation was done. The hearing did not improve. She had rheumatic fever at 12; was in bed for 1 week and confined at home for 10 days. At the age of 13 she had an attack of paratyphoid fever. She had never gotten along well at school, had always been backward in her studies and at the age of 16 was in the 8th grade. She had never menstruated.

She was $55\frac{1}{2}$ inches tall and weighed 109 pounds. The span was 54 inches. Symphysis to vertex measured $27\frac{3}{8}$ inches; symphysis to sole $27\frac{7}{8}$ inches. There was somewhat excessive girdle adiposity and the breasts were very large. There was very little hair on the genitalia and no hair in the axilla. There was psoriasis on the hands and feet. The tonsils were large and the postcervical glands were slightly enlarged; otherwise the general physical examination gave no findings of importance. The eye grounds were normal, showing no evidence of retinal degeneration.

Gynecologic examination showed a small and conical cervix and a retroverted and antiflexed uterus. The diagnosis was genital hypoplasia of moderate degree.

The ear examination showed evidences of bilateral chronic catarrhal otitis media and marked loss of hearing due to nerve deafness.

Roentgen ray studies showed a sella possibly slightly smaller than average (Fig. 1). The bones of the skull otherwise were normal. No changes were observed in the bones of the forearms and wrists (Fig. 2). There was a possibility of slight thymic enlargement. Basal metabolism was +24 per cent. Sugar tolerance figures were 121 mg. before administration of glucose, 192 mg. at 1 hour and 123 mg. at 2 hours afterward. The blood Wassermann was negative. The urine was normal. Blood count was recorded as hemoglobin, 80 per cent; red blood cells, 4,650,000; white blood cells, 14,000; the differential count showed polymorphonuclears, 57 per cent; lymphocytes, 39 per cent, and monocytes, 4 per cent. The blood pressure averaged 110 systolic and 60 diastolic. Temperature, pulse and respirations were normal. The patient remained under observation

for about a year and a half and received thyroid, pituitary and ovarian substance during that period. Beneficial results were questionable. She did not increase in height; for a time the weight was slightly reduced, but later returned to the previous level; scanty menses occurred on three occasions at very irregular intervals; there was a slight growth of hair over the genitals but none in the axilla. Hearing did not improve and there was no improvement in schoolwork. Toward the end of this period of observation tonsillectomy was performed with satisfactory convalescence but apparently without benefit to her hearing.*

CASE 2.—A sister, aged 26 years, likewise presented adiposity, mental deficiency, deafness and insufficient menstruation. Like the other child she was born slightly prematurely. She weighed 6 pounds at birth. She was a delicate infant; teethed at the normal age; talked at about 14 or 15 months; and began walking at about 2 years. Deafness was discovered at the age of 10 or 11. Adenoid operations were performed at the age of 13 and again at 17. The mother thinks that the hearing improved slightly after the second operation. During infancy and in childhood the mother states that this child had some sort of spells; her body would "stiffen out," but since menstruation she had had none of these attacks. Menstruation did not begin until about 17. It had been fairly regular but never sufficient in amount. She was operated on for appendicitis at the age of 20. She never got along well at school, was in the 6th grade at the age of 17 and then quit.

She was 5 feet tall and weighed 142 pounds. There was a high-arched palate, girdle adiposity and very large breasts. The mother stated that she had always been stout and also mentioned that the difficulty in hearing was especially with the left ear and that this was true of the first child as well. This patient spoke with difficulty and had a kind of muffled speech. The general physical examination gave no findings of importance other than those mentioned. The patient presented herself only once and would not permit further study.

The 2 middle children of this family were slight. The hearing was good and they seemed perfectly normal.

Discussion. From a study of our cases and a review of the literature it seems clear that the Laurence-Biedl syndrome is a congenital and familial form of cerebral adiposity associated with mental deficiency, genital dystrophy, retinitis pigmentosa and frequently polydactylism. The recorded cases resemble one another very closely, a distinctive feature being the familial occurrence. In fact, Boenheim[7] states that cases can be placed in the Laurence-Biedl group only if familial. He also calls attention to the fact that one or another of the chief symptoms may be absent and that not all cases show the complete picture of the Laurence-Biedl syndrome as above described. In addition he mentions *hardness of hearing* as a cardinal characteristic of the syndrome.

The early students of the subject considered a lesion of the pituitary gland responsible; Biedl and Raab[8] discussed the development of the disorder from a mechanical standpoint suggesting that a high and massive dorsum sellæ (a skeletal defect which they consider

* The patient was last heard from July, 1931. The height remained the same; weight, 124 pounds; hearing had not improved, and the menses still were very irregular.

similar to that of polydactylism) interferes with the flow of an energizing secretion from the pars intermedia of the pituitary gland through the stalk of the infundibulum to certain metabolic and genitotropic centers at the floor of the midbrain.

Just as the main objection to the pituitary gland origin of this syndrome was the absence in many cases of any evidence that could be interpreted as pointing to a lesion of this gland, so the same objection holds to the Biedl and Raab hypothesis; no evidence of a high or massive dorsum sellæ has been found in many cases of the fully developed syndrome.

Ornsteen[4] offers a more satisfactory explanation based upon the embryologic development of the hypothalamic region of the diencephalon. He holds that a genetic defect of the prosencephalon (forebrain) is responsible for the adiposogenital dystrophy, retinitis pigmentosa and mental deficiency (a cerebral genotypic unit character) and that the polydactylism, skull deformities, atresia ani and other occasional anomalies are present only through the accidental coupling of somatic genotypic unit characters.

Because of the occasional association of congenital (nerve) deafness with the Laurence-Biedl syndrome (Boenheim) and also because nerve deafness frequently acts as a mutual equivalent for retinitis pigmentosa in the hereditary transmission of the condition (Nettleship[9]) it would seem that the cases here recorded represent a variation of the Laurence-Biedl syndrome in which deafness takes the place of retinitis pigmentosa. One would be inclined, therefore, to seek the same embryologic explanation for both, namely, developmental failure due to a genetic defect of the prosencephalon. However, nerve deafness cannot be explained on the same basis as the optic atrophy with retinitis pigmentosa; the entire inner ear including the otocyst (anlage of the cochlea, the definitive organ of hearing, and the ganglion of the auditory nerve) take their origin in the hindbrain rather than the forebrain. Nevertheless, there seems to be more to the association than a coupling of somatic genotypic unit characters which is the explanation Ornsteen offers for the occurrence of unrelated anomalies in the Laurence-Biedl syndrome such as polydactylism and atresia ani. Nettleship,[9] in a thorough study of retinitis pigmentosa from a hereditary standpoint stated that the commonest associated degeneracy occurring in subjects of retinitis pigmentosa is congenital deafness of various degrees. In another study[10] he states that retinitis pigmentosa, progressive nerve deafness and feeblemindedness or idiocy seem capable of acting as mutual equivalents or substitutes. In the state of our present knowledge, therefore, we must allow that nerve deafness cannot be explained embryologically as an equivalent for retinitis pigmentosa in the Laurence-Biedl syndrome but that further embryologic investigations may throw more light on the occurrence.

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REVIEWS.

THE FIVE-YEAR PROGRAM OF THE COMMITTEE ON THE COST OF MEDICAL CARE, ADOPTED FEBRUARY 13, 1928. PUBLICATIONS Nos. 1 to 12. Pp. 39. Washington, D. C.: The Committee on the Cost of Medical Care. Price, 25 cents to $1.00.

ADMITTEDLY one of the most pressing problems of the practice of medicine in this country is the high cost of medical care for the middle classes. It was a wise prevision, then, to create this agency to study the problem in a comprehensive way over at least a 5-year period, while the personnel of the rather large committee ensures that the task will be well done. The support of the Carnegie Corporation, the Milbank Memorial Fund, the Russell Sage Foundation and the Twentieth Century Fund has made possible a minimum outlay of over $250,000. Thus far the following topics have been reported on: The Extent of Illness and of Physical and Mental Defects Prevailing in the United States; A Survey of Statistical Data on Medical Facilities in the United States; Hospital Service for Patients of Moderate Means; Medical Care for 15,000 Workers and Their Families; A Survey of the Medical Facilities of Shelby County, Indiana: 1929; Capital Investment in Hospitals; Private Group Clinics; A Survey of the Medical Facilities of the City of Philadelphia: 1929; A Study of Physicians and Dentists in Detroit: 1929; A Survey of the Medical Facilities of San Joaquin County, California: 1929; The "Municipal Doctor" System in Rural Saskatchewan. E. K.

EGYPT. THE HOME OF THE OCCULT SCIENCES, WITH SPECIAL REFERENCE TO IMHOTEP, THE MYSTERIOUS WISE MAN AND EGYPTIAN GOD OF MEDICINE. By T. GERALD GARRY, M.D., M.Ch., M.A.O., M.B.E. Pp. 193. London: John Bale, Sons & Danielsson, Ltd., 1931. Price, 7/6d.

IMHOTEP, the Wazir of King Zoser of the 3d Dynasty, has of recent years received so much "publicity"—perhaps more than in an equal number of previous centuries—that he is in danger of acquiring the false values that often attend the spot light. While it is in no way implied that the excellent work of Sethe, Hurry, Dawson and others affords basis for exaggerating this apparent superman who was later deified and replaced Thoth as the chief

Egyptian God of Medicine, yet the present critical analysis by one who appears to be qualified for the task is as timely as it is interesting.

The chapters on magic and medicine among the ancient Egyptians in the same way present a healthy scepticism to those who are wont to find that recent scientific achievements are but rediscoveries of phenomena already known by the ancients.

As to Imhotep, himself, it seems clear that only by possible future discoveries, if at all, can it be decided whether he was of human origin later deified, possibly another name for Zoser himself, of divine origin or possibly that his name ("He who comes in peace") was merely an epithet of Ptah. He may still prove to be our earliest known physician or earliest God of Medicine; but as yet he can hardly be said, in Osler's phrase, "to be the first figure of a physician to stand out clearly from the mists of antiquity." Rather should we still agree with Hurry, "Nothing is known of his special work as a physician." E. K.

THE GREAT PHYSICIAN. A LIFE OF SIR WILLIAM OSLER. By EDITH GITTINGS REID. Pp. 299; 10 illustrations. New York: Oxford University Press, 1931. Price, $3.50.

THE continuing interest in this great humanist suggested that, in spite of the mass of biographic material that has been published in the past decade and of the masterly two volume Life by Harvey Cushing, a shorter story with more sweeping brush strokes would be desirable. Mrs. Reid consented to undertake the difficult task and the result shows the wisdom of the conception and of the choice of author.

With enough of the bare facts as a framework to carry a connected chronologic sequence of events, the author has built up a loving picture of the spirit of "a transcendently beautiful life." With a minimum of duplication of previously published biographic material, and with due regard for Osler's scientific achievements, she has painted a portrait that vibrates with life and must capture even future generations with its charm. The 18 pages of "The End"—already beautifully told by Cushing—will rank high as literature, while to those who loved her hero they raise emotions too poignant for contemplation unrelieved by action. Whatever the position in medical history assigned to Osler by posterity—and none would have been more careless of the result than the man himself—it will doubtless be largely determined by the beneficent interest in and influence exerted on his fellows. This tribute, then, should not only bring pleasure to many not yet acquainted with this "beloved physician," but should be valuable in preserving for

posterity the essence of an elusive spirit whose greatness might otherwise be more difficult to appreciate than that of lesser souls with perhaps more concrete achievements. E. K.

THE NOTE-BOOK OF EDWARD JENNER. With an Introduction on JENNER'S WORK as a Naturalist. By F. DAWTREY DREWITT, M.D. (OXON.), F.R.C.P., formerly on the Committee of the British Ornithologist's Union, and on the Council of the Zoölogical Society of London. Pp. 49; 1 illustration. New York: Oxford University Press, 1931. Price, $1.25.

THIS manuscript note-book of the great vaccinator, covering the period 1787–1806, has been in the possession of the Royal College of Physicians since 1888, where it has evoked so much interest that it was thought desirable to make it available to a larger circle of readers. It throws an interesting light on Jenner's activities as a naturalist and comparative pathologist. The short but important notes on the habits of the cuckoo form the basis for his paper before the Royal Society on which his fame as a naturalist chiefly rests. The longer, industrious notes on hydatid cysts afford accurate and vivid descriptions, but served to support Jenner's erroneous belief, "long ago conceived" that hydatids were the cause of "true tuberculous consumption." The lack of microscopic aid is but too obvious. In the notes on dog's distemper, no definite conclusions were reached, and indeed could hardly have been expected at that time. E. K.

OXFORD MONOGRAPHS ON DIAGNOSIS AND TREATMENT. Edited by HENRY A. CHRISTIAN, M.D., SC.D., LL.D., Hersey Professor of the Theory and Practice of Physic, Harvard University. Ten volumes. New York: Oxford University Press, 1928–1931. Price, $100 set of 10 volumes. (The first 9 volumes, of which No. VII is still incomplete, appeared in the course of the last 3 years and have been reviewed in a previous issue of this Journal: 1931, **181**, 270.) VOL. X. THE DIAGNOSIS AND TREATMENT OF PNEUMONIA. By CAMPBELL P. HOWARD, B.A., M.D., C.M., F.R.C.P. & S. (CAN.), Professor of Medicine, McGill University, and Physician to the Montreal General Hospital. Pp. 263.

THIS volume, which in the original prospectus of this set of books was entitled "Diagnosis and Treatment of Acute Respiratory Infections including Pneumonia," is apparently to be limited to a consideration of pneumonia. It is as yet incomplete: only lobar pneumonia has been covered, a section on bronchopneumonia is to

be issued later. While in the other volumes of the series diagnosis and treatment have received the major emphasis and space, the section on pneumonia has been written in the manner and scope of a "system" article. There are chapters on (1) History, Incidence and Etiology; (2) Infection and Immunity; (3) Morbid Anatomy; (4) Symptomatology; (5) Physical Signs; (6) Complications; (7) Clinical Types and Diagnosis; (8) Prognosis and Prophylaxis; (9) Treatment. The material is very well and for the most part adequately presented. Empyema, however, especially the management and differentiation of borderline cases, deserved a fuller discussion.

R. K.

THE CAUSATION OF CHRONIC GASTRO-DUODENAL ULCERS. A NEW THEORY. By J. JACQUES SPIRA, M.R.C.S. (ENG.), L.P.C.P. (LOND.). With an Introduction by SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., Regius Professor of Physic in the University of Cambridge. Pp. 78. New York: Oxford University Press, 1931. Price, $2.50.

IN the introduction it is stated: "The thesis here presented is of considerable practical interest, for it incriminates a food factor as the responsible cause. . . . Stated briefly the argument is as follows: fat when introduced into the stomach regularly causes regurgitation of the duodenal contents, including bile, into the stomach; and bile-salts, when mixed with the acid gastric contents, damage the mucous membrane of the stomach." While the author gives much collateral material in support of his theory it is to be regretted that he gives so little evidence of his own. Under "experimental evidence" he offers no original observations, while the "clinical experience" offered is practically limited to 5 inadequate case reports and the statement that "for over a period of more than 10 years, a treatment based entirely on this conception of the disease has given me remarkedly consistent and uniformly satisfactory results."

R. K.

MANUAL OF SURGERY. VOLUME I: GENERAL SURGERY. By ALEXANDER MILES, M.D., LL.D., F.R.C.S., ED., Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S., ED. and ENG., Professor of Surgery, University of Edinburgh. Pp. 574; 176 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, $3.80.

THE eighth edition of this well-known surgery is marked by the addition of Mr. D. P. D. Wilkie to the editorial staff. In addition there have been some twenty of the younger men of the Edinburgh

faculty whose aid has been enlisted as "coadjutors in revision of the text." The revision has been thorough and has brought the text up to date in most respects. The previous arrangement of the material has been followed in the new edition. Excellent chapters on repair, inflammation, suppuration and ulceration are given. Surgical tuberculosis, syphilis and tumors are discussed in more detail than is usual in most American texts. The chapters on the various systems, as the bloodvessels, lymph vessels and glands, nerves, bones, etc., are preceded by short summaries on the anatomy and physiology of the tissue. The chapter on diseases of bones and joints is especially complete.

The book is simply and clearly written and fairly well illustrated. The therapeutic suggestions adhere somewhat to the older methods, but the work well represents the excellent teachings of the Edinburgh school.

L. F.

BEDSIDE INTERPRETATION OF LABORATORY FINDINGS. By MICHAEL G. WOHL, M.D., Associate Professor of Experimental Medical, Temple University Medical School. With an Introduction by JOSEPH MCFARLAND, M.D., SC.D., Professor of Pathology, University of Pennsylvania. Pp. 321; 133 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $6.00.

THE author's preface emphasizes the fact that it is the purpose of this book to evaluate, rather than to describe in detail, those laboratory tests most used in present day diagnostic medicine. A few of the more widely accepted methods are described in detail, as one would find them in any physiologic chemistry, and other tests necessitating specialized laboratory technique are considered only from a clinical standpoint. The author experienced some of the natural difficulties in the selection of material for such a brief but comprehensive work; for example, he gives a rather extensive survey of parasitology and hematology, and quite sketchy discussions of dermatology and bacteriology. However, the real value of this work lies in its sound criticisms of the inaccuracies and errors in clinical interpretation of those laboratory procedures considered of greatest usefulness to the general practitioner.

S. S.

PRACTICAL ZOÖLOGY. By ROBERT W. HEGNER, PH.D., Professor of Protozoölogy, Johns Hopkins School of Hygiene and Public Health. Pp. 561; 332 illustrations. Revised edition. New York: The Macmillan Company, 1931. Price, $1.80.

THIS is an elementary text-book of zoölogy intended for use in secondary schools, and material presented covers the entire animal

kingdom. Space, of course, is limited but the attempt has been made to present facts that will focus the attention of beginners on the more common representations of the various animal groups. The economic value of different groups of animals meets with special attention. The text is supplemented by numerous illustrations, references to readily accessible sources, a glossary and an index.

H. R.

BOOKS RECEIVED.

NEW BOOKS.

Progressive Medicine, Vol. IV, December, 1931. Edited by HOBART AMORY HARE, M.D., LL.D., assisted by LEIGHTON F. APPLEMAN, M.D. Pp. 456; 76 illustrations. Philadelphia: Lea & Febiger, 1931.

Practical Endocrinology. By HENRY R. HARROWER, M.D. Pp. 704. Glendale, Calif.: Pioneer Printing Company, 1931. Price, $5.00.

Conquering Arthritis. By H. M. MARGOLIS, M.D. Pp. 192; 2 illustrations. New York: The Macmillan Company, 1931. Price, $2.00.

Osler and Other Papers. By WILLIAM SYDNEY THAYER, M.D., LL.D., DR. HON. SC.D., F.R.C.P. IRE., HON., Professor Emeritus of Medicine at the Johns Hopkins University. Pp. 386. Price, $3.50.

Les Maladies de L'Esprit et Leurs Medecins. Du XVI^e^ au XIX^e^ Siècle. By M. LAIGNEL-LAVASTINE and JEAN VINCHON. Pp. 377; illustrated. Paris: Norbert Maloine, 1930.

Publications of the Committee on the Cost of Medical Care. By various authors. For titles of the 12 pamphlets thus far published see review in this number of the JOURNAL. Washington: The Committee on the Cost of Medical Care, and Chicago: The University of Chicago Press, 1928–1931. Price for each publication: 25c to $1.00.

NEW EDITIONS.

Practical Morbid Histology. By ROBERT DONALDSON, M.A., M.D., CH.B. (EDIN.), F.R.C.S.E., D.P.H., Sir William Dunn Professor of Pathology in the University of London, etc. With Foreword by SIR HUMPHRY ROLLESTON, BART. G.C.V.O., K.C.B., M.D., Regius Professor of Physics, University of Cambridge. Pp. 487; 214 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1931.

Bacteriology for Nurses. By HERBERT FOX, M.D., Director of the William Pepper Laboratory of Clinical Medicine in the University of Pennsylvania; Pathologist to the Zoölogical Society of Philadelphia, etc. Pp. 311; 91 engravings and 7 colored plates. Fifth edition thoroughly revised. Philadelphia: Lea & Febiger, 1931.

"With the opinion that it is now desirable for nurses to know more microbiology, the author has added a number of directions for the growth and study of bacteria, protozoa and metazoa, for the use of the microscope, skin tests, blood typing, etc. The subject is presented in an accurate, dignified manner. The illustrations are appropriate and well done."

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Postvaccination Encephalitis.—Encephalitis following vaccination is a disease of unknown etiology that has been recognized only in the last seven years. Following the original observation of Lucksch, who reported 3 cases of nervous manifestations following vaccination that occurred in Czechoslovakia, some 600 other cases have been reported from Europe. ARMSTRONG (*Ann. Int. Med.*, 1931, **5**, 333) says that in the United States 51 proven or probable cases have been recorded for the 10-year period just prior to 1931, 41 cases occurring in the last 3 years, a rough average of about 1 case for each 350,000 vaccine points sold in the United States during this time. These figures are probably not representative of the actual frequency of the disease in the United States. For example, 3 cases of encephalitis following vaccination have been admitted to the Charity Hospital, New Orleans, in the past 9 months. In Europe the large number of cases that were reported in 1926–1927 is a matter of record. The etiology of this type of encephalitis is not definitely known. French investigators believe that it is the vaccine virus directly which is implanted in the central nervous system to produce the disease. They have substantiated their contention by reasonably well-controlled experimental methods. The German students of encephalitis, on the contrary, lean toward the idea that the vaccine virus primarily is not the cause of the disease; rather that the encephalitis develops as a result of the presence of a virus, in a given community, which is of unknown origin and which is lying dormant, to become activated when the individual is vaccinated. The proof that the Germans have deduced does not seem to be as definite as that obtained by the French in support of their idea concerning the cause of the disease. Confirmatory evidence of the German idea might be obtained from one of the statements made in Armstrong's

paper, that the heaviest incidence in the United States occurred in a city of about 450,000 inhabitants. These cases were vaccinated by five different vaccinators, who employed different measures, but all of whom employed the same manufacturer's vaccine, but this same manufacturer distributed this lot of vaccine all over the United States and no other cases of encephalitis were reported. In the diagnosis of the condition there is one important feature which should be accentuated, and that is that the encephalitis symptoms develop almost invariably in from 10 to 14 days after vaccination. If the central nervous symptoms arrived 17 to 24 days after vaccination then the symptoms are probably due to postvaccination tetanus. The most important one single measure of prevention lies in the vaccination of children in the first year of life. Postvaccination encephalitis rarely occurs among infants vaccinated at this age period. Vaccinations performed in later life produce the great bulk of the cases of encephalitis following vaccination. In Europe it has been customary to employ multiple insertions in the technique of vaccination. The Rolleston Commission recommends a single small implantation of virus. It has also been suggested that dilutions of the virus be employed in vaccinating half-grown children and young adults rather than employing full-strength virus.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Postoperative Pulmonary Atelectasis.—BROWN (*Arch. Surg.*, 1931, **22**, 976) says that the importance of the bronchial secretions in producing postoperative atelectasis and in determining the specific type of atelectasis which ensues is stressed. Experimental and clinical observtions are compared and are found to agree. Thick tenacious sputum is noted to plug the larger bronchi, whereas thiner sputum tends to greater dispersion and a blocking of the finer bronchi and bronchioles, thereby producing a scattered lobular atelectasis. The impression is gained that spinal anesthesia predisposes to postoperative pulmonary atelectasis.

Ollier's Disease—Unilateral Chondrodysplasia.—BROMER and JOHN (*Am. J. Roentgenol.*, 1931, **26**, 428) believe that a review of the literature does not determine whether this disease, extremely disabling because of its unilateral retardation of bone growth, is an unusual manifestation of the condition known as hereditary deforming chonrodysplasia, as Keith, Stocks, Hale and others believe, or is a distinct entity, as Ollier and others have claimed. The fact that Cleveland's case was under observation for a sufficient length of time to show that the affected long bones are growing, and that the lesions are undergoing delayed

ossification and spontaneous healing, tends to support Ollier's theory. The 26 cases here collected are all similar and, as Cleveland stated in his summary, the clinical picture of each case is so like the others that even if there is no clear-cut pathologic differentiation from a much larger class of cartilaginous dystrophies, they seem to fall into a definite clinical group. A study of more patients from infancy to maturity and more experimental work such as that of Bentzon may ultimately be of assistance in answering the question as to whether or not Ollier's disease is a separate entity.

Varicose Ulcers.—WRIGHT (*Brit. Med. J.*, 1931, **3690**, 561), says that varicose ulcers and their complications all result from loss of balance between arterial and venous systems of the leg. This balance can be restored in two ways, by lying down and by reinforcing the skin with an elastic support. In the cases due to varicose veins great improvement can be made by obliterating and in bad cases also ligating the varices, so that 75 per cent of ulcer cases can be cured and remain cured without any support but the elasticity of the patient's own skin. Ulcers of the leg will always be with us until we find a way of preventing femoral thrombosis after operations, fractures and childbirth, but they will diminish in number because of the simplicity of the injection treatment for early varicose veins. By this method of treatment there is a certain way of curing all gravitational ulcers. The larger ulcers, formerly acknowledged to be incurable, can now be readily cleared up by this method even when of the gigantic dimensions of 180 square inches ($1\frac{1}{4}$ square feet). The author holds that it is one of the most wonderful things in Nature to see the ulcer which may have started a quarter to a half century ago begin to throw up its granulations, flatten out its margins, pull in its edges and epithelialize in the way described so well by John Hunter many years ago.

Rapid High Temperature Deaths Following Biliary Tract Surgery.—CONNELL (*Ann. Surg.*, 1931, **94**, 363) states that the fatal high temperature reaction following biliary tract surgery appears to be a definite clinical entity. Seventeen such cases occurring in 72 deaths after biliary tract operations are analyzed. It would seem rational to consider the syndrome as a metabolic, chemical or allergic reaction or to a nervous phenomenon, the exact nature of which is unknown. Instances of spontaneous recovery (what might be termed abortive) do occur but present no characteristic feature differentiating them from the fatal cases. Treatment in the absence of etiologic factors is symptomatic. Therapeutic efforts in the "abortive" cases fail to give a clue to effective treatment. A review of postoperative records in laparotomies for conditions other than biliary tract disease failed to show similar temperature reactions. Further study it is hoped will clear up the subject and develop an effective therapy.

Fascia Lata Grafts.—HORSLEY (*Ann. Surg.*, 1931, **94**, 410) claims that dead alcohol-preserved fascia of an ox and living autogenous fascia react similarly in the peritoneal cavity and in the abdominal wall of the dog. In no instance does encapsulation occur. Kangaroo tendons soon become encapsulated and are absorbed more quickly in the

abdominal wall than in the peritoneal cavity. The fascias, both dead, alcohol preserved of the ox and the autogenous, atrophy and stretch when placed in the peritoneal cavity, but not in the abdominal wall. For pyloric occlusion chromicized kangaroo tendon is much more satisfactory, forming total occlusion for over 6 months in the dog and causing fewer adhesions than the fascia. The living fascia seems to occlude the pylorus several weeks longer than the dead alcohol-preserved fascia of the ox. If infection is present both the living and the dead alcohol-preserved fascia of the ox are broken down and absorbed, while chromicized kangaroo tendon shows a high degree of resistance to infections. The alcohol-preserved fascia of the ox does not react in man as it does in the dog, but is quickly absorbed and loses its tensile qualities, while the autogenous fascia lata in man apparently retains its strength.

THERAPEUTICS

UNDER THE CHARGE OF
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AND
SOMA WEISS, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Action of Digitalis on the Ventricular Portion of the Human Electrocardiogram.—WINTERNITZ (*Ztschr. f. Krebsforsch.*, 1931, **33**, 452) summarizes a carefully controlled series of investigations upon the effects of digitalis on the *Q–R–S* and *T* complexes of the electrocardiogram in some 500 patients. Of this group 143 proved available because their observations were free from all disturbing factors. In 13 per cent no influence upon the ventricular portion of the electrocardiogram was observed despite the definite presence of therapeutic or toxic action of the drug. Conversely, changes in the electrocardiogram were observed without any other evidence of digitalis action. The most frequent change in the electrocardiogram was an alteration in the amplitude of the waves, affecting either the initial complexes (*Q–R–S*) or the *T* wave. It was especially observed that the amplitude of the waves was increased by digitalis in those cases showing low voltage prior to treatment. This reversible low voltage is of prognostic significance as indicating the existence of a transitory myocardial impairment, and such cases as present it are to be distinguished sharply from those showing the irreversible form. In the present group one-half of the patients presented the more favorable reversible type of low voltage. The author calls attention to the fact that changes in the amplitude of the waves must be studied critically in order to eliminate those due to various extra cardiac factors, such as change in position of the heart, rotation of the electrical axis and the like, due to alterations in the position of the diaphragm, and changes due to variations in the accuracy of the application of the

electrodes. All of these factors were eliminated in the group of cases from which the author draws his conclusions. He points out, however, that the wide divergence of opinion observed in the literature may possibly be explained on the basis of neglect of the control of these factors. Depression of its amplitude or inversion of the *T* wave may be quite independent of the action of digitalis, as indicated by others, where it is due to one-sided ventricular preponderance. In such cases digitalis has the tendency to alter the *T* wave and the *S–T* line in the opposite direction to that of the initial complex, thus positive *T* waves are increased in their positiveness and negative waves become deeper. A depression of the *T* wave, therefore, is by no means a constant digitalis effect. This occurred in only 24 per cent of the cases, as a phenomenon independent of a preëxisting axis deviation, while digitalis exaggeration of the amplitude of the *T* wave which is dependent upon the direction of the initial complex occurred in 34 per cent of the cases. In these two groups toxic manifestations were present in 59 per cent of the first group and in only 37 per cent of the second. There was no instance observed among the 143 cases in which digitalis caused prolongation of the *Q–R–S*, while in 3 instances showing preexisting prolongation digitalis led to some shortening of the time or to its return to normal. In 1 case right-sided bundle-branch block disappeared under the influence of digitalis. There is evidence for believing, therefore, that digitalis may improve intraventricular conduction. From all of his studies the writer suggests that digitalis tends toward restitution of that form of the electrocardiogram which was present in the given patient prior to the development of cardiac failure.

The Treatment of Migraine With Extract of the Anterior Lobe of the Pituitary.—It is a common observation that women suffering from frequent and severe attacks of migraine are often completely free from such attacks during pregnancy, only to have them begin again at the cessation of lactation. KLAUSNER-CRONHEIM (*Deutsch. med. Wchnschr.*, 1931, **57**, 1455), acting upon this observation and the studies of Aschheim and Zondek, which showed the presence of large quantities of anterior lobe hormone in the blood of pregnant women, treated 10 patients by the oral administration of an active anterior lobe extract. All the patients were suffering from severe migraine of long standing and unrelieved by previous therapy. Of the 10 patients 7 were either entirely relieved or showed marked diminution in their pains while 3 were unaffected. Of the 7 patients in whom improvement or relief took place 1 was unable to continue the treatment because of the production of severe menstrual disturbance, while 2 more showed increase in menstruation and a shortening of the intermenstrual interval which, however, did not prevent the continuation of treatment. Investigation showed that in those patients successfully treated by this method there was no effect upon the elimination of sodium chloride indicating that the beneficial action was quite different from that following the restriction of chloride intake. The author believes that in these cases of migraine there is probably some toxic substance circulating in the blood which is fixed or destroyed by the anterior lobe hormone. Its failure to relieve certain patients suggests, however, that this is not always the case and leaves the question of the cause of migraine unexplained in these nonresponsive patients.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Calcium and Phosphorus Metabolism of Infants Receiving Undiluted Milk.—VAN KIRK (*Am. J. Dis. Child.*, 1931, **42**, 1090) presents 70 observations of the calcium and the phosphorus intake, output and retention of a group of infants fed undiluted milk. The average daily retention of calcium ranged from 0.070 gm. per kilogram at 2 months to 0.044 gm. per kilogram at 10 months of age. The average daily retention of phosphorus ranged from 0.040 gm. per kilogram at 2 months to 0.027 gm. per kilogram at 10 months of age. The calcium-phosphorus retention ratio ranged from 1.3 to 2.3 with an average of 1.75: 1. The average calcium content of the blood was 12 mg. per 100 cc. with 10 as the lowest value obtained and the average phosphorus content was 6.3 mg. per 1000 cc. with 5.4 as the lowest value observed. Measurements of calcified areas showed no widening of the distal end of the shaft of the radius and an excellent rate of ossification of the carpal centers. Roentgengrams of the wrists showed certain irregularities in the growth of bones frequently associated with mild rickets. Owing to the large amounts of calcium and phosphorus retained by these infants, the consistently high blood values, the excellent growth of the carpal centers, and the occurrence of the rachitic changes in summer as well as in winter, the question is raised whether these slight irregularities of growth at the epiphyseal junctions unaccompanied by rarefication are rachitic or whether they may be normal accompaniments of the rapid increase in the rate of growth.

Undulant Fever in Children.—ANDERSON AND POHL (*Am. J. Dis. Child.*, 1931, **42**, 1103) state that many authors in describing undulant fever of bovine origin have mentioned the slow, poorly defined, insidious character of the onset. Weakness, anorexia, fever, chills and profuse sweats are usually the prominent symptoms as the disease becomes established. Subacute migrating pains in the extremities, joints, back and muscles, and headache are mentioned. The physical examination elicits no characteristic signs. A roseolar, macular, scaling eruption has been observed in a few cases. Loss of weight, abdominal tenderness, enlarged spleen, slight anemia and slight leukopenia are found in a variable number of cases, with continued fever the only consistent feature. The disease runs a variable course from weeks to years, averages about 3 months, and gradually subsides, usually without serious sequelæ. In none of the 3 cases, the subject of this report, was it possible to make a definite clinical diagnosis of undulant fever. The physical findings were exceedingly irregular and largely negative, but the persistent fever prompted the submission of blood specimens for agglutination tests. In each case it was possible to trace the infection to the cows supplying the milk which these children habitually used. These 3 cases all ran short courses of from 7 weeks to 8 months. The children were at no time seriously ill, and apparently all recovered

without complication or sequelæ. Typical undulation of fever was not observed. There were periods of high fever which followed exertion, but the fever subsided after rest.

Nutritional Edema.—Weech and Ling (*J. Clin. Invest.*, 1931, **10**, 869) consider the serum protein deficiency in relation to various types of edema, both experimental and clinical. They call attention to other factors and in particular to the rôle of several inorganic salts in modifying the effect of protein deficiency alone. In a series of patients suffering from nutritional edema, who were studied during both the active and the convalescent stages, it was found that when the level of serum albumin was greater than 2.9 gm. per 100 cc. edema was never observed, and that when the level fell below 2.5 gm per 100 cc. edema was invariably present. The correlation with total serum protein, although not so close, was sufficient to indicate a critical level for edema close to 5 gm. per 100 cc. Serum globulin was exceedingly variable as decreased, normal and increased values were all found in association with edema. Decreased globulin generally occurred only when the albumin was also decreased and this was usually present in association with edema. No relation of cause and effect was considered to exist between lowered globulin and edema. The results of metabolism observations were noted on 2 of these patients. In both cases the combined administration of sodium chlorid and sodium bicarbonate led to rapid gain in weight with marked increase in edema and depression of chlorid excretion in the urine. In one of these cases these effects could not be duplicated, after feeding an adequate diet had resulted in a return to normal of the serum protein. It is pointed out that it is impossible to offer an exact explanation of all the effects observed, although it is indicated that the results are in harmony with the view that the cation sodium is more intimately related with the causation of edema than the anion chlorid.

The Effect of Large Doses of Irradiated Ergosterol on Nitrogen, Calcium and Phosphorus Metabolism in Rats.—Kern, Montgomery and Still (*J. Biol. Chem.*, 1931, **93**, 365) found macroscopic and microscopic evidence of the accumulation of much calcium in the kidneys in growing rats receiving large daily doses of viosterol. Chemical analyses of those organs revealed the deposition of calcium to be much greater in females than in males. Viosterol in larger doses increases the absorption of calcium from the intestine. The excretion of calcium in the feces decreases and the excretion in the urine is greatly increased. To a lesser degree there is also a diminished fecal elimination of phosphorus. Ergosterol irradiated in alcohol produces greater disturbance of the calcium metabolism of growing rats than ergosterol either irradiated in ether or irradiated dry, on the basis both of actual weight of ergosterol fed and of the vitamin D content of the samples. It is believed that the medium in which the ergosterol is irradiated plays an important part in the development of toxicity. The nitrogen excreted in the urine seemed to have been entirely within the normal range, being affected mainly by the level of food intake. Whatever changes may occur in the way of deposition or absorption of bone in rats fed large amounts of viosterol, analyses of the leg bones of these animals show normal content of calcium, phosphorus and carbon dioxid.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Amebiasis Cutis.—ENGMAN and MELENEY (*Arch. Derm. and Syph.*, 1931, **24**, 1) reëmphasize the fact that ulceration of the skin may at times be due to an ameba in some cases identified as Endameba histolytica. The cases reported fall into four groups: (1) Those following the drainage of an amebic abscess of the liver; (2) those following the drainage of a lesion of the appendix or other areas of the lower portion of the intestine; (3) those about the anus associated with amebic colitis; and (4) those without any direct connection with the viscera. The authors in describing the clinical picture of amebic ulcers, particularly stress the rapidity of spread of the ulcerative process, the overhanging edge from under which pus can be expressed, and the surrounding erythematous terrain. Usually motile amebæ can be identified in fresh preparations from the ulcers but at times are discoverable only in fixed smears and sections. Emetine hydrochlorid is the accepted method of treatment.

Sensitizations.—SULZBERGER and MAYER (*Arch. Derm. and Syph.*, 1931, **24**, 537) contribute a timely article on the discrepancies in results obtained by an attempt to duplicate previous experimental work and point out that the factor of geographical localization of the experiments performed has never been given sufficient weight in the analysis of the data involved. The authors believe that differences in the race, feeding and housing of the test subject or experimental animals are factors which may entirely alter results obtained by similar methods at widely separated points. They have observed, for example, that guinea-pigs reacted differently when sensitizations with the same brand of neoarsphenamine were attempted in Breslau, Zurich and New York, the results varying from 98 per cent successful sensitizations in Breslau to none in New York. These differences were constant in spite of experiments carried out with care to provide for identical technique. A study of the modifying factors disclosed among other things that the diet of the experimental animals was of decided importance, green fodder inhibiting and dry fodder favoring sensitization. The authors wisely counsel that the knowledge and consideration of these facts may alter premature decisions on contradictory experimental results and account in part for differences in clinical, epidemiological and seasonal fluctuations noted under varying environment.

GYNECOLOGY AND OBSTETRICS

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Carcinoma of the Cervical Stump.—Those who favor the performance of total hysterectomy as a routine base their preference on the fear of the later development of cancer in the retained stump of the cervix which is left after the supravaginal operation. Various estimates have been made as to the frequency of this condition but on account of the comparatively small number of cases which are seen in any one clinic it is difficult to arrive at a representative figure. This subject has been investigated by MAYO and MAYO (*Ann. Surg.*, 1931, **93**, 1215) who studied the records of 99 patients with cancer of the retained cervix who had been seen in the Mayo Clinic during the preceding 20 years. A larger number of cases was found within the first 2 consecutive years after subtotal hysterectomy than in any 2 years thereafter, although more than 50 per cent occur 3 years or more after subtotal hysterectomy. The condition must be considered serious because ultimately so few patients are cured, perhaps because the disease is not diagnosed until it is far advanced. They feel that at the primary operation the total hysterectomy should be the operation of choice since they can show a mortality of 1.8 per cent for this operation as against 1.2 per cent for the subtotal hysterectomy in two series large enough to be of importance. If the surgeon fears to perform the total operation but nevertheless believes that the retained cervix may be a future menace to the patient, they advise the performance of the subtotal operation, followed in 10 or 12 days by some method of removal of the cervix, such as enucleation of the canal or destruction of the cervical canal by cautery. While their argument seems rather convincing, nevertheless their figures show that in spite of the wealth of material at their disposal with consequent extensive experience, the total operation has a higher mortality in their hands as in the hands of nearly every other gynecologist or surgeon.

Renal Irradiation for Ureteral Fistula.—When in the course of a pelvic operation the ureter has been injured and the damage recognized at once, the operator must quickly decide as to what measures must be taken to alleviate the injury. The ideal policy when possible is to perform immediate anastomosis of the cut ends or to transplant the upper end into the bladder, while some operators are content to merely ligate the ureter in order to cause atrophy of the corresponding kidney. Many ureteral injuries however, are not recognized until several days after the operation, when a leakage of urine from the vagina

reminds the gynecologist that all is not well. Under such conditions a secondary operation may be quite a hazardous procedure and for this reason the suggestion was made several years ago that the easy and safe method of handling such a situation was to irradiate the kidney of the affected side with sufficient dosage to cause its atrophy and thus a bloodless cure could be obtained. As a result of his experiences with this procedure OTTO (*Zentralbl. f. Gynec.*, 1931, **55**, 1529) concludes that irradiation of the kidney should only be considered as a means of treatment when the function of that kidney is largely destroyed providing, of course, that the functional capacity of the opposite kidney is good. In such cases good results may be looked for. When the kidney corresponding to the injured ureter has good function he believes that it is much more desirable to implant the ureter into the bladder or bowel since irradiation will frequently fail to cause atrophy of normal renal tissue.

OPHTHALMOLOGY

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Extraocular Muscle Paralysis Following Spinal Anesthesia.—FAWCETT (*Minnesota Med.*, 1931, **14**, 648) reports 2 cases of external rectus paralysis following spinal anesthesia with novocain. In the first patient the paralysis developed on the thirteenth day postoperative and cleared up completely in 13 days In the second patient the paralysis developed on the twelfth day postoperative and was still present at the end of 17 months. This complication of the spinal anesthesia is relatively rare. Reber reports 5 cases in a series of 2000 anesthesias. The external rectus is the muscle most frequently involved. In 88 cases reviewed by Blatt the fourth never was involved in 4, the third in 6 and the sixth in 78. The interval between the anesthesia and the onset of the paralysis varies between 3 days and 3 weeks. The prognosis is favorable. In most cases the paralysis disappears in from 1 to 3 weeks. In a few it persists longer. The onset is usually accompanied by photophobia, headaches and dizziness. The etiology of the paralyses is still a matter of conjecture. It seems most probable that they are caused by an elective toxic action of the injected drug. However, they may have their basis in a mild localized meningitis or a localized hemorrhage. Van Lier has demonstrated swelling of the nuclei of the ganglion cells after spinal anesthesia. It is known that the injected drug often diffuses up around the medulla and base of the brain in appreciable concentration. So it is possible that the ocular muscle paralyses are due to degeneration of the ganglion cells.

Hereditary Optic Atrophy (Leber's Disease).—KUHN (*Arch. Ophthal.* 1931, **5**, 408) reports a case of hereditary optic atrophy (Leber's disease) in which an exploratory operation was performed on the chiasmal region. The patient was a man, aged 25 years, who complained of a sudden loss of vision first in the left and later in the right eye. Vision in the right eye was 20/100 and in the left the ability to count fingers at 12 inches. Perimetric studies revealed central scotomata, relative in the right eye and absolute in the left. The scotomata involved the temporal more than the nasal part of the fixation area. Ophthalmoscopic examination revealed bilateral mild optic neuritis with commencing atrophy in the left eye. General physical, laboratory and neurologic examinations were all negative. The sella was small and partially bridged. There was a definite familial history of sudden loss of central vision. An elder brother had relative scotomata and two maternal uncles had been similarly affected. Exploration of the chiasmal region showed no lesion except a mild arachnoiditis. However, the vision improved gradually, and three months after operation was 20/50 in the right eye and 9/200 in the left. Two months later the vision in the right eye fell to 20/200. Encephalograms and ventriculograms made at this time failed to reveal any pathologic condition near the optic chiasm but did suggest a chronic encephalomyelitis with some obstruction in the region of the fourth ventricle but without internal hydrocephalus. Seven months after the first operation the vision of the right eye was 9/200 and that of the left eye 8/200.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The So-called Bursa Pharyngea in Man: Its Origin, Relationship With the Adjoining Nasopharyngeal Structures and Pathology.—Plenty of proof of the correctness of Pasteur's aphorism—"in the fields of observation chance only favors the mind which is prepared"—can be found in such happy coincidences as Galileo and the swinging lamp in Pisa's cathedral; Newton and the falling apple; Jenner and the milk-maid's cowpox; Darwin and the Beagle's cruise; Beaumont and Alexis St. Martin's gastric fistula. Assisted by Meyers and Shirazy, DORRANCE (*Arch. Otolaryngology*, 1931, **13**, 187), taking advantage of an unusual opportunity for detailed study of a bursa pharyngea in an adult with cleft palate, presents an exhaustive account of developmental, anatomic and clinicopathologic of pharyngeal bursa. Evidence is produced to show that the true bursa pharyngea, as encountered in adults, represents the persistence of the embryonal bursa and is to be looked upon as an independent structure which, although in intimate relationship with a coexistent adenoid, is not to be regarded simply as a medium recess of the pharyngeal tonsil or as necessarily bearing any relation to cleft palate. Its anatomic position is characteristic—in

the midline of the pharynx just anterior to the upper border of the superior constrictor muscle. Clinically, the bursa pharyngea is of interest. Forty-five years ago Dantzig's Tornwaldt called attention to certain inflammatory processes of the bursa associated with systemic disturbances. As Dorrance says, "When his opinion is considered in the light of modern medicine one finds that in spite of errors due to overenthusiasm he was anticipating the era of focal infection." In any event Tornwaldt's work stimulated in a neglected anatomic field and emphasized the embryologic complexity and clinical importance of the nasopharynx.

An Aural Syndrome of Hepatic Origin.—To Louis we owe largely the demonstration of the "numerical method" as a valuable instrument of investigation. The guiding motto of his life was "'Ars medica tota in observationibus'"—in carefully observing facts, carefully collating them, carefully analyzing them." Accurately to get knowledge of any disease it is necessary to study a large series of cases and to go into all particulars. A correlation of the occurrence of any one of these with all of the other data may reveal something of causal significance or diagnostic importance. Accordingly, from the mass of information acquire by a thorough and comprehensive survey in a large diagnostic clinic primarily designed to study diseases of the ductless glands, DRURY (*Ann. Otol., Rhinol. and Laryngol.*, 1931, **40**, 415) has expiscated a series of 120 cases exhibiting ear involvement associated with hepatic dysfunction. The syndrome includes, in their order of frequency, such symptoms as deafness, tinnitus, vertiginous symptoms, headaches, fatigue and nausea. A characteristic audiometric finding is mentioned. The writer believes the syndrome to be due primarily to a long-standing toxemia of hepatic origin. Clinical improvement follows proper care and treatment.

RADIOLOGY

UNDER THE CHARGE OF

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Coccidioidal Granuloma: Roentgen Diagnosis.—This disease, which attacks lungs, bones and soft tissues, and pathologically, clinically and roentgenologically resembles tuberculosis closely, deserves the systematic and complete review given by CARTER (*Am. J. Roentgen. and Rad. Therap.*, 1931, **25**, 715). The first case was reported from Buenos Aires in 1892; the second and third cases from California in 1894. In this country, approximately 80 per cent of all cases reported were Californian in origin, but scattered cases have been noted from Washington, Arizona, New Mexico, Colorado, Kansas, Nebraska, Missouri, Illinois, South Carolina and Pennsylvania. It is suspected that many cases go unrecognized. The disease is produced by a specific

fungus, oïdium coccidiodes, which in its adult form is a spherule 15 to 40 microns in diameter, and which multiplies by endosporulation. Infection, it is believed, may occur through the abraded skin, through the alimentary canal and through the respiratory tract. Pulmonary invasion is considered to be most frequent. Pathologically characteristic of the disease is the production of submiliary, miliary or larger nodules which resemble tubercles. The nodules may caseate and subsequently liquefy or they may suppurate from the beginning. The lesions are nearly always progressive, but may heal eventually. Abscesses may occur in the soft tissues; lymph nodes tend to be involved early. In the lungs may be found extensive miliary lesions, nodular consolidations with caseation, abscesses or massive consolidations. The lesions of bone are essentially those of a destructive osteomyelitis. The clinical manifestations vary with the mode of infection and the situation of metastatic lesions. Frequently the onset is respiratory, with fever, cough and malaise. The disease may run a rapid course with early death. If the pulmonary symptoms subside or the primary infection is in the skin, the disease may become chronic for weeks, months or years. Positive diagnosis rests on finding the specific organism; a long search may be necessary. Treatment is unsatisfactory. Colloidal copper has given good results in a few cases. From the roentgenologic standpoint Carter has surveyed 50 cases. Ninety-four lesions were found in bone. They arose mostly in the region of cancellous bone and the process was predominantly destructive, although in a minority of instances bone production was noted. Adjacent joints were involved in only 28 cases. This seems to afford a mark of distinction from tuberculosis, in which the joint tends to be involved early. Sites and bones commonly invaded included the ribs, the malleoli of the tibia and fibula, tarsus, tuberosity of the tibia, the ulna, scapula, clavicle, patella, etc. Lesions arising in malleoli and other bony prominences seem to be rather suggestive of coccidioidal granuloma. The chest was examined in 37 cases and was involved in all but one. Miliary lesions were evident in 19; they were usually general and with localized accentuations in some portion of the lung, most frequently on the right side. Hilar thickening was evident in 31 cases and a definite mediastinal mass in 17. Parenchymatous infiltration distinct from miliary dissemination, was present in 32 cases, or 90 per cent; it varied from slight clouding to dense consolidation. Pleural involvement with effusion occurred in some cases. Compared with tuberculosis, the outstanding features of pulmonary coccidiosis are the high incidence of mediastinal involvement, miliary lesions and hilar thickening, the less fibrosis and cavitation, and the general softness and vagueness of the shadows. The advanced lesions resemble the caseous or pneumonic type of tuberculosis, but with less tendency to cavitation.

Radiation Therapy in the Treatment of Cancer of the Mouth and Lips.—MARTIN (*Radiology*, 1931, **16**, 881) has had satisfactory results from radiotherapy by both radium and Roentgen ray. In his series there were 108 cases without evidence of metastasis at the time of treatment. Later 4 cases developed malignant nodes in the neck and died. The remaining 104 cases were well after 5 years. Eleven cases had definite involvement of lymph nodes when treatment was begun; all these patients died from cancer.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Successful Socialization and Compensation in Manic-depressive Psychosis.—HINSIE (*The Psychiatric Quarterly*, 1931, **5**, 2, 312) remarks that with the advent of Freudian psychoanalysis, patients began to understand many of the causal relationships between their symptoms and the "buried complexes" allied to the instinctive realm—that it was observed that there was a series of closely identified relationships of psychial factors extending from consciousness deep into the unconscious field. Insight of this nature is decidedly apart from the insight that enables the patient to appreciate his mental phenomena only in terms of "morbid" or "normal." The former might be referred to as primary and the latter as secondary insight. When secondary insight is well developed and especially when it is supported by a desire on the part of the patient to expand the insight to the primary degree, psychotherapy may accomplish meritorious results. Further, the author remarks that it is a well established observation that subjects with a manic-depressive psychosis achieve periods of remission during which their "morbid" manifestations are relegated to the background. These individuals in the phase of remission, attain certain grades of social integrity, but there is not the psychological harmony that insures future integration at the higher levels. Relapses occur with much frequency. The manic-depressive patient is not altogether unlike the schizophrenic patient who exhibits periodically in his mental disorders. In both instances, there is more or less complete return to the prepsychotic level. And, states the author, adjustment and integration are closely associated. When an individual coördinates his several capacities (physical, physicochemical, sensori-motor, psychologic and social), in the direction of a reasonable goal, and at the same time temporarily subordinates other issues, it may be said that that individual is well adjusted. The 6 cases presented were under active treatment and management for about 2 years and for about 5 years, they were not interviewed. As a result of the instituted work upon the patients, it was found that some of the patients responded very favorably. Others were appreciably assisted to adjust at a higher level than that to which they had formerly adapted themselves. There was a third group that was not at all benefited. This latter group consisted of patients that refused treatment of any nature. In addition, the author felt that in most cases the question of socialization and compensation is a question also of the socialization and compensation of his environment. An individual's career is made up not only of his own instinctive cravings, but also of the cravings of others. The individual's reactions are a resultant of instinctive processes, not only of those aris-

ing within himself, but also of those that come to him from without. Hence, when socialization and compensation are under consideration, one must inevitably take into account the patient and several personalities that he has incorporated within himself. This implies a clear understanding of the emotional streams as they converge from several angles upon the subject under treatment.

Radiothermic Treatment of General Paralysis.—HINSIE and CARPENTER (*Psychiatric Quarterly*, 1931, **5**, 2, 215) present a preliminary report of their findings in the radiothermic treatment of 17 cases of general paralysis. Eleven of these cases have left the hospital definitely improved, 5 are still in the hospital, having but recently completed their treatment, and 1 case is dead, having died shortly after the course of treatment started. The plan of approach was to produce the temperature curves of inoculated malaria in a series of patients with general paralysis. If these conditions were met, it was considered that there might then be more or less suitable control material by which the efficacy of radiothermic treatment might be computed. All patients were adults. Each was given treatment consisting of 70 hours of temperature. They noted the following facts: (1) The treatment was tolerated well; (2) the agent that induces the temperature rise is under immediate control; (3) the temperature rise may be gauged to meet the cardiovascular-nephritic capacity of the patient; (4) the patients usually show improvement while they are undergoing treatment; (5) there is a loss of 5 to 10 pounds of weight, which is promptly regained upon termination of the treatment; (6) there is a mild anemia, a reduction of hemoglobin, an increase of the polymorphonuclear cells, and the spinal cell count is reduced during the treatment—all swinging within normal limits upon termination of the treatments; (7) the blood solids and chlorids all remain within normal limits during the therapy; (8) the blood sugar tends to rise slightly during the radiothermic course. Concerning the Wassermann findings in the blood and spinal fluid, the authors make no note—stating that it is too early to form any opinion as yet, concerning this phase of their work.

Mental Factors that Affect School Abilities.—LINE (*Ment. Hyg.*, 1931, **15**, 2, 255), remarks that present day educational research is showing the very marked and healthy influence of the mental hygiene movement. The genetic picture of childhood is being made more meaningful, more complete, because of the growing realization that a thorough understanding of that picture is necessary to a preventive program; and the influence of the school on the mental growth of the child is the particular emphasis now being made by those who are endeavoring to integrate educational research into the mental hygiene program. It is universally agreed that the genetic method is the one that is most ideal in arriving at the necessary foundation for a mental hygiene program. The case study method is a second best, or is a means whereby the genetic picture may be more immediately clarified for present guidance. He asks if we do not select our categories of observation largely—sometimes entirely—in terms of behavior, rather than in terms of psychologic (functional), manifestations; or if we do not sadly confuse our behavior concepts with the more subtle concepts of mental hygiene. He then states that there is a distinct differ-

ence in the implications of the two classes: that one really intends to refer only to descriptive aspects of behavior, to incidents that are observable by others; the second goes much deeper, and implies the functional picture. And by confusing this distinction, our conception of the genetic method tends to become that of a series of quantitative records. But in essence, the genetic method is undoubtedly qualitative, and must ultimately arrive at a qualitative interpretation of the cross-sectional picture of the child as he now is—a picture that can, of course, be meaningful only insofar as its antecedents and functional consequents are known. The evaluation of educational progress is ultimately qualitative, in the sense that a child is rated as superior or inferior to another in respect to a given "ability" or "trait." The basis of determining that rating may be more or less "objective," and may involve mathematical quantities, but fundamentally the entity postulated and measured, is an inherent mental quality or aspect. The qualitative correlation of educational abilities can be made to some extent in a more scientific way than is the case with behavior categories. The author asks whether one might not expect that an analysis of causes of success or failure in certain broad lines of activity would reveal other, more subtle, psychologic deviations, which have been overlooked in our training programs, and which have played a vital part in the genesis of special disabilities. And it is in this connection that one of Spearman's leads seems to have a significant application. After a completely satisfying objective demonstration of the general nature of intelligence, certain other functional unities are isolated. Spearman, after an interpretative supplement, puts forward the tentative hypothesis of "mental energy" to account for intelligence; but this energy displays marked individual differences, not only in quantity, but also in quality. The variation in "inertia" corresponds to the statistically demonstrable factor of "perserverations;" and differences in terms of fatigue, recuperation manifest themselves, during continuous and concentrated mental work, as a greater or less oscillation or fluctuation in efficiency. These additional variables make the psychological analysis of a child much more meaningful and scientific than before; and the relationship between deviations along the new axis thus demonstrated and mental functioning in the classroom would seem to be worthy of investigation.

PATHOLOGY AND BACTERIOLOGY

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The Endocarditic Process (Valvulitis) in Childhood.—De Vecchi (*Arch. Path.*, 1931, **12**, 49) reports his findings from a careful histologic analysis of the heart valves of 42 children. Postmortem diagnosis of this condition is usually based on the macroscopic appearance of the valves. Such evidence, however, is fallacious as valves that are healthy

to the naked eye may show microscopic changes that are inflammatory in nature. This is especially true in the case of infants as the valvular apparatus is very delicate and the initial changes are difficult to detect. The lesions observed in areas macroscopically healthy consisted of desquamation of the valvular endothelium, sometimes with hyalinization and necrosis of the adjoining valvular tissue, accompanied by a lymphocytic infiltration of the deeper layers and a histiocytic reaction in the subendothelial layers. The histiocytic reaction was usually well marked and was not necessarily accompanied by endothelial desquamation. The essential nature of the endocarditic process is partly degenerative and partly inflammatory. The formation of thrombotic vegetations, he considered, is a secondary phenomenon which may be entirely absent, but he did not give much attention to disturbances in capillary circulation as affecting the local resistance and the deeper histiocytic reaction. The inflammatory reaction in the initial stages of the process he found to be always of the same type, whatever the stimulus, bacterial or toxic. In the later stages it varies with the nature of the microorganism and the "resistance" of the subject. The inflammatory processes that develop in the valves of young children affected by various toxic infective diseases, he emphasized, are of particular importance, as their further development may give rise to the establishment of valvular defects, the mode of origin of which has hitherto been obscure.

Hemolytic Streptococci in Scarlet Fever and Epidemic Septic Sore Throat.—HERZBERG (*Monatschr. f. Kinderh.*, 1929, **43**, 328) studied some 2200 throat swabs taken at monthly intervals from 170 inmates of a children's hospital and tuberculosis clinic for the presence of hemolytic streptococcus. The average findings of hemolytic streptococci were for children (2 to 15 years) 40 per cent, for those of the tuberculosis clinic 60 to 70 per cent, for infants 10 to 15 per cent. Single swabs from 150 inmates of a tuberculosis sanitarium taken in January gave 75 per cent and from 100 school children in July gave 17 per cent positive for hemolytic streptococci. The positive findings increased as a rule in the damp and cold months from September to December, but this was not constant. Twenty-six clinical cases of scarlet fever in the children's hospital comprised 17 from the tuberculosis clinic, 8 in age group 2 to 15 years, and 1 infant. He found no relationship between the incidence of hemolytic streptococci and the occurrence of scarlet fever, and concludes that none exists. No record is given that the strains of hemolytic streptococci were tested for toxin production by means of toxin-antitoxin injections. This study would have been more valuable if such toxin determinations had been done although the specificity of the toxin of scarlet fever strains is discounted by the work of WHEELER (*J. Preven. Med.*, 1931, **3**, 181) who asserted that "it is impossible by the methods now available to separate the streptococci associated with epidemic septic sore throat and scarlet fever into definite groups which bear a specific relation to the particular type of infection induced." In one outbreak of streptococcus infection typical strains of Streptococcus epidemicus identical in all their reactions, including skin antitoxin tests, were isolated from the milk of one cow, from the throats of patients with septic sore throat and also from the throats of scarlet fever patients.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Antigenic Value of Scarlet Fever Streptococcus Toxin Modified by the Action of Formalin.—VELDEE (*U. S. Pub. Health Rep.*, 1931, **46**, 693) notes that various authors have reported on the successful use of scarlet fever toxin in the prevention of that disease. He also points out the disadvantages of the methods in general use following in the footsteps of Ramon who has prepared a harmless yet potent immunizing agent against diphtheria. Several workers have used formalin to produce an analogous product for scarlet fever. The author's own work has shown that a very high percentage of immune persons can be secured by the use of three doses of his toxoid, whereas five doses of unmodified toxin are required to bring about a similar result. The unpleasant reactions are much fewer when toxoid is used than when the unmodified toxin is employed.

Experimental Addiction of Animals to Opiates.—KOLB and DUMEZ (*U. S. Pub. Health Rep.*, 1931, **46**, 698) present the results of an extensive series of studies on monkeys in which attempts to induce addiction by the use of morphin, codein and heroin were made. Monkeys were killed by subcutaneous injections of morphin sulphate as low as 85 mg. per kilo of body weight, and very severe symptoms with sickness lasting several days were caused by smaller doses, but 1 animal survived 125 mg. per kilo, and the minimum fatal dose was not accurately determined. Young and small monkeys survived larger doses per kilo than older and larger animals. Seven milligrams of heroin per kilo of body weight killed the majority of monkeys that had not previously been given a toxic dose. Some that had previously received a toxic dose of an opiate survived 8 mg. per kilo. Some monkeys that survived a toxic dose of morphin, heroin or codein were less severely affected by slightly larger doses given from a week to a month afterward. No monkey survived as much as 80 mg. of codein phosphate per kilo of body weight, and 1 died from 60 mg. per kilo. Codein caused convulsions frequently, heroin much less often and morphin never. By daily administration of morphin, heroin and codein monkeys were made tolerant of increasingly large doses. After 8 or 9 months 200 mg. per day of morphin caused less severe immediate symptoms than 10 to 40 mg. did during the first six weeks; 39 mg. of heroin caused less severe symptoms than did 4 mg. at first; 110 mg. of codein caused less severe symptoms than did 10 mg. in the beginning. One animal that

was started on morphin was kept on it or on heroin for 52 months. Gradual deterioration in general health was caused by daily administration of codein, morphin and heroin. Codein was decidedly the most harmful and heroin the least. Morphin caused marked dependence, shown by a crouching posture, facial distortion, hypersensitiveness, fall in temperature and, in 1 case, death on withdrawal of the drug. Heroin caused less dependence and codein was not definitely shown to produce dependence. Monkeys made tolerant to large doses of morphin, heroin or codein were tolerant to large doses of all three drugs, but the dependence produced by morphin and heroin was not satisfied by codein. Tolerance was almost completely lost in about 2 weeks after withdrawal of the drugs, and the monkeys improved in health and general appearance during the remainder of the period of abstinence. Monkeys abstinent for 6 weeks or 2 months after having received daily doses of morphin or heroin for 16 months or more were more sensitive and less resistant to the drugs when injections were started again than they had been in the beginning. Some of these cases reacted with marked spasticity.

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Anesthesia in Ameba.—L. V. HEILBRUNN (from the Laboratory of Zoölogy, University of Pennsylvania). In many respects, the common ameba is an excellent form for the study of anesthesia. Because of its continuous movement, it is easy to establish criteria of anesthetic action. Moreover, the viscosity of the ameba protoplasm can readily be studied, and one can thus obtain information regarding the effects of anesthetics on the colloidal properties of the living substance. By studying the two common types of ameba, Ameba dubia and Ameba proteus, it is possible to study the physical properties both of the internal protoplasm and of the outer cortex or plasmagel. In Ameba dubia, it is a simple matter to determine the viscosity of the internal protoplasm (plasmasol) by the centrifuge method (Heilbrunn, 1929). On the other hand, when Ameba proteus is centrifuged, one may determine the speed with which granules or crystals are moved through the plasmagel. A complete picture of both the internal and the external protoplasm is thus obtained.

Ameba is readily anesthetized by potassium salts in dilute solution, and the potassium ion has a very marked liquefying action on the plasmagel. Magnesium has a less pronounced anesthetic action, and its effect on the plasmagel is less pronounced. The anesthetic action of both potassium and magnesium ions is antagonized by calcium. Preliminary studies with fat solvents indicate that in this type of anesthesia also, the plasmagel becomes more fluid. Certain other agents also stop the movement of the ameba by liquefying the plasmagel. These agents include heat and ultraviolet radiation.

The Reducing Power of Glomerular Urine and Blood Plasma from the Frog.—A. M. WALKER, J. R. REISINGER, and E. H. ELLINWOOD (from the Laboratory of Pharmacology, University of Pennsylvania). A micro modification of Sumner's dinitrosalicylic acid method was described which makes it possible to analyze 0.2 c.mm. of known glucose solutions with a maximum error of 3 mg. per 100 cc. The method is applicable to similar amounts of frog plasma, the results being in close agreement with those yielded by the Hagedorn-Jensen method. Thirty-two experiments have been completed on intact frogs in which the reducing substance content of glomerular urine and plasma have been measured. The mean difference between the two fluids was 2.1 mg. per 100 cc. with a mean deviation of 3. It was concluded that the reducing substance content of the two fluids is identical—a result in harmony with previous experiments from this laboratory which have indicated the function of the glomerulus to be one of filtration.

A series of 5 frogs received preliminary injections of phloridzin before the glomerular collections were made. In no one of these instances did the glomerular fluid contain more reducing substances than the plasma. It was therefore concluded that the glomeruli played no active part in the glycosuria which followed the use of this drug.

Cerebrospinal fluid has been collected for 10 frogs by cisternal puncture and analyzed by the method described. The mean reducing substance content was 13 mg. per 100 cc. less than that of plasma simultaneously collected.

Effect of Pituitary Removal on the Survival of Decerebrate Cats.—H. C. BAZETT (from the Laboratory of Physiology, University of Pennsylvania). Recent work has tended to discredit the idea that the pituitary is essential to life.[1] In view, however, of the presence of accessory pharyngeal glands of anterior lobe type, of a pars tuberalis extending over the infundibulum,[2] and of the identification of secretory cells of anterior lobe character extending into the tuber cinereum,[3] it is certain that no complete removal on a physiologic basis has been attained without a complicating nerve injury. Symptoms are ascribed by some to the pituitary, by others to nerve lesions (particularly diabetes insipidus and adiposity) and Bourquin[4] even attributes diabetes insipidus to irritation of a chemical mechanism existing in the corpora mamillaria. The decerebrate cat is of value in that the hypothalamic region may be left *in situ* while isolated from the rest of the brain, so that it could produce effects via chemical but not via nervous channels.

The technique of obtaining chronic decerebrate cats described in 1922[5] has been improved, first, by using "Nembutal" as an anesthestic to diminish hemorrhage during and after operation; second, by keeping the animals in a warm moist room (21° to 22° wet bulb, 24° to 26° dry bulb) to decrease risks of infection and dessication. Rectal temperature is controlled by electrical resistance thermometers connected to a Leeds and Northrup recording potentiometer. By a system of selective switches and relays the temperature of each of a series of 4 animals is sampled for 1½ minutes every 9 minutes, and a heating light below the animal is automatically switched on or off as required.

The average survival time of 8 control animals, in which the pituitary and neighboring isolated brain was intact, has been greater than 11.8 days (min. 3.6, max. 28.5) even though several animals have been

deliberately killed for other purposes after 1 week. When the pituitary and the hypothalamic brain area have been removed, the average survival time (8 animals) has been 4.33 days (min. 1.25, max. 6.25). Death has occurred preceded by an initial but subsiding polyuria, loss of weight gradually decreasing in rate, a terminal rapid respiration without respiratory infection (also noted earlier[6]), and a tendency to vomit, but there has been little or no tendency to the convulsive movements observed in earlier experiments.[5]

Two animals died with this typical symptomatology without the pituitary being removed; in one (life 4.25 days) the brain stump was negligible but the pituitary intact, in the other (life 5 days) the pituitary was demonstrated histologically normal but the neighboring brain tissue was soft and degenerated.

The following provisional conclusions may be drawn:

1. Under the régime described with a food intake of 200 cc. of milk a day some chemical effect of the pituitary and surrounding brain tissue is essential for survival.
2. The chemical functions of this area are more readily attained when the anatomical relationship of the pituitary to the brain stem is not disturbed.
3. The hypothalamus itself is probably not essential, for survival has been observed in one case in its absence.[5]

My thanks are due to Mrs. Friedman, who assisted in developing the technique, to Dr. Friedman for making histologic sections of the pituitary, and to Mr. A. Afford and H. Goslyn for their careful nursing of the animals; also to the Abbott Laboratories for supplying "Nembutal."

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The Effect of Toxic Doses of Irradiated Ergosterol Upon the Composition of Rat Bones.—J. H. Jones and G. M. Robson (from the Laboratory of Physiologic Chemistry and Laboratory of Pathology, University of Pennsylvania). The premise that irradiated ergosterol, at least in large amounts, can increase the absorption of calcium (and possibly phosphorus) from the intestinal tract and also mobilize this element from body tissue is being gradually substantiated. The most obvious source of body calcium is the skeleton, and several attempts have been made to show that inorganic constituents have been withdrawn from the bones during irradiated ergosterol intoxication. The results of chemical analyses of bone have been somewhat contradictory and misleading due primarily to the use of growing animals. Since there was a normal increase in the percentage of bone ash of the controls during the experimental period no reliable basis for comparison was available. In other cases insufficient vitamin D preparation was given to produce a toxic condition or so much was administered that the animals died before irradiated ergosterol had opportunity to exert any influence on the bones.

In the following experiments 36 rats divided into 3 groups were used. When placed on experiment the animals varied in age from 68 to 138 days. Two groups were used as controls, the first of which was killed at the beginning and the other at the end of the experimental period. Sufficient irradiated ergosterol was given to the experimental animals to cause toxic symptoms followed by death within 6 weeks to 2 months after the beginning of the feeding. The right femur from each animal was removed and analyzed for ash. The distal end of the other femur and the proximal end of the corresponding tibia were removed and fixed for histologic examination. Before ashing, the right femora were Roentgen-rayed in a group on one plate. The ash analyses revealed that, in general, there was a marked decrease in the percentage of bone ash; the maximum reduction being about 10 per cent when compared with a litter-mate control. Upon histologic examination it was found that the cortex of the shaft had become very porous. The porosity was due to a complete destruction and resorption of organic as well as inorganic matrix, and the spaces so formed were filled with marrow. Under the high power magnification many osteoclasts were discernible which would indicate an osteoclastic destruction of the bone. There was no evidence of a simple chemical removal of the inorganic salts. The densities of the roentgenograms were determined with a densitometer.* It was found that the densities of the negatives of the bones of the experimental animals were about 10 per cent greater than those of either of the control groups. Since the measurements were made on the negative, the densities of the bones themselves would be correspondingly decreased. There were a few discrepancies between the chemical, histologic and Roentgen ray findings but these occurred among the younger animals. All experimental animals above 100 days of age showed a loss of bone matrix as shown by chemical, histologic and Roentgen ray studies. No evidence was obtained to indicate that this action is specific for irradiated ergosterol. It is possible that chronic intoxication caused by other substances may produce similar effects.

* We wish to thank Professor Charles Weyl and Mr. Reid Warren of the Moore School of Electrical Engineering for making the densitometer determinations.

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